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Intense exercise for survival among men with metastatic castrate-resistant prostate cancer (INTERVAL-GAP4): A multicentre, randomised, controlled phase III study protocol

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Keywords:	physical activity, tumour biology, immune function, inflammation, disease progression

STUDY PROTOCOL

Intense exercise for survival among men with metastatic castrate-resistant prostate cancer (INTERVAL-GAP4): A multicentre, randomised, controlled phase III study protocol.

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Short Title: *Exercise and Survival of Prostate Cancer.*

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ABSTRACT

Introduction

Preliminary evidence supports the beneficial role of physical activity on prostate cancer outcomes. This phase III randomized controlled trial (RCT) is designed to determine if supervised high-intensity aerobic and resistance exercise increases overall survival in patients with metastatic castrate-resistant prostate cancer (mCRPC).

Methods and Analysis

Participants (n=866) must have histologically documented metastatic prostate cancer with evidence of progressive disease on androgen deprivation therapy (ADT; defined as mCRPC). Patients can be treatment naïve for mCRPC or on first line androgen receptor (AR)-targeted therapy for mCRPC (i.e. abiraterone or enzalutamide) without evidence of progression at enrolment; and with no prior chemotherapy for mCRPC. Patients will receive psychosocial support and will be randomly assigned (1:1) to either supervised exercise (high-intensity aerobic and resistance training) or self-directed exercise (provision of guidelines), stratified by treatment status and site. Exercise prescriptions will be tailored to each participant's fitness and morbidities. The primary endpoint is overall survival (OS). Secondary endpoints include time to disease progression, occurrence of a skeletal-related event, or progression of pain; and degree of pain, opiate use, physical and emotional quality of life, and changes in metabolic biomarkers. An assessment of whether immune function, inflammation, dysregulation of insulin and energy metabolism, and androgen biomarkers are associated with OS will be performed, and whether they mediate the primary association between exercise and OS will also be investigated. This study will also establish a biobank for future biomarker discovery or validation.

Ethics and Dissemination

Validation of exercise as medicine and its mechanisms of action will create evidence to change clinical practice. Accordingly, outcomes of this RCT will be published in international, peer-reviewed journals, and presented at national and international conferences. Ethics approval was first obtained at Edith Cowan University (ID: 13236 NEWTON), with a further ten investigator sites since receiving ethics approval, prior to activation.

KEY WORDS

physical activity, tumour biology, immune function, inflammation, disease progression

Trial Registration:

Prospectively registered, 10th March, 2016: https://clinicaltrials.gov/ct2/show/NCT02730338

STRENGTHS AND LIMITATIONS

- This is the first randomised controlled trial (RCT) to examine exercise and overall survival in men with prostate cancer.
- This is a novel multi-national, multi-centre and multidisciplinary RCT, with 24 months of supervised tapered to self-managed exercise with behavioural and psychosocial support, compared to self-directed exercise with psychosocial support alone, in men with metastatic castrate resistant prostate cancer (mCRPC).
- The study proposed will determine the efficacy of an individually tailored, progressive and autoregulated aerobic and resistance exercise program, supervised by accredited exercise physiologists (or equivalent) in addition to usual medical care; in parallel with a health economics analysis to assess the health benefits, additional costs, and potential savings of including exercise therapy as standard of care for men with mCRPC.
- The study has a translational team to investigate biomarkers associated with three candidate pathways: systemic inflammation, insulin/glucose metabolism, and androgen biosynthesis; to study how they mediate the association between exercise and overall survival, and to establish a blood, urine and tissue biobank for future biomarker discovery or validation.
- The outcomes of this Phase III RCT are limited to men with mCRPC.

INTRODUCTION

An emerging body of literature supports the role of exercise during cancer treatment as a therapy which leads to improved outcomes, both in quality of life and potentially disease control.[1] Identifying and evaluating low-toxicity adjuvant interventions, such as exercise, that can be combined with standard therapy to improve outcomes for men with prostate cancer is a high priority and has the potential to have a large impact on the clinical and public health burden of prostate cancer.

In 2006, Galvão, et al.[2] reported that resistance exercise and programs with resistance and aerobic exercise improved physical function and quality-of-life in men without metastases on androgen deprivation therapy (ADT) for prostate cancer. These results were expanded in a subsequent report Galvão et al.[3] showed that combined resistance and aerobic exercise reversed the loss of muscle mass and improved quality-of-life in prostate cancer patients on ADT. In addition, Kenfield et al.[4] reported that vigorous aerobic exercise after prostate cancer diagnosis was associated with a 60% lower risk of fatal prostate cancer and a 49% lower risk of all-cause mortality among men initially diagnosed with localized disease. The dose-specific effect of larger quantities of vigorous physical activity having greater survival benefit has also been reported by Friedenreich et al.[5] In addition, one prospective study reported that resistance exercise was associated with a 33% lower risk of all-cause mortality in male and female cancer survivors while overall physical activity was not.[6] These findings emphasize the potential benefits of exercise as an adjuvant treatment in prostate cancer. However, data on exercise and cancer survival to date have been from observational studies in which bias from confounding and reverse causation are of concern. Thus, a randomized controlled trial is needed to test whether exercise, in particular higher intensity aerobic exercise and resistance exercise, impacts overall survival in men with prostate cancer. Additionally, treatment-related fatigue is a common side effect in men with advanced prostate cancer and exercise may decrease fatigue and increase adherence to treatment regimens.[7-9]

While the prevailing view among patients and clinicians has been that exercise may be problematic for cancer patients with advanced disease, recent research has demonstrated tailored resistance and aerobic exercise to be well-tolerated, safe, and effective for improving physical structure and function.[10] Moreover, in patients with bone metastases, a highly tailored exercise prescription implementing a modular-multimodal approach and avoiding excessive loading of the skeletal lesions has been demonstrated to be safe and effective.[10]

There are many potential mechanisms by which exercise may lower risk of prostate cancer progression.[1,11,12] Exercise influences all hormonal systems in the body, including key hormones relevant to prostate cancer, such as testosterone, growth hormone, insulin and insulin-like growth factor-1 (IGF-I). The androgen receptor (AR) and its transactivation by ligand are one of the most important determinants of prostate cancer progression. Measurements of serum androgens (including its receptors and binding proteins) provide an important biomarker for the effectiveness of androgen deprivation and prostate cancer progression. The effects of exercise on serum androgen levels remain elusive to date,[13] with current studies limited by low patient numbers and inadequate methods for measuring testosterone levels in the low ranges seen in men on ADT.[14] This is especially true with the newer cyp17 inhibitors, such as abiraterone. Additionally, high levels of inflammatory biomarkers are associated with an increased risk of prostate cancer-specific mortality[15] and exercise is known to lower levels of circulating inflammatory biomarkers (e.g., IL-6) in elderly populations. [16,17] Increased physical activity may also produce epigenetic modulations that may inhibit tumor cell proliferation, such as altering histone deacetylase pathways. Exercise and dietary changes may also lower cholesterol, which epidemiological studies have suggested are associated with decreased risk of prostate cancer and progression of prostate cancer. [18,19] Together, these observations suggest that exercise interventions with prostate cancer patients may improve disease outcomes and quality of life. However, given the highly suggestive observational findings, a randomised control trial is warranted to establish clear causal relationships and guide clinical recommendations.

The primary objective of the GAP4 Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-GAP4) study is to determine if high-intensity aerobic and resistance training plus psychosocial support increase overall survival (OS) compared to self-directed exercise (non-supervised exercise recommendations) plus psychosocial support, in patients with metastatic, castrate-resistant prostate cancer (mCRPC). OS was chosen as the primary endpoint because it has clear biological, clinical, and public health significance and is a validated endpoint for approval of new treatments among men with mCRPC. Additionally, OS data can be obtained with minimal loss to follow-up through review of medical and death records.

Secondary objectives are to compare time to disease progression, time to first occurrence of a symptomatic skeletal-related event, time to progression of pain, degree of pain, and opiate use, physical and emotional quality of life, and change in levels of biomarkers of inflammation, energy metabolism, and androgen metabolism between the

supervised exercise and self-directed exercise groups. It will also be determined as to whether biomarkers of immune function, inflammation, energy metabolism, and androgen metabolism are associated with OS among men with mCRPC, and the extent to which these biomarkers mediate the hypothesized association between high-intensity aerobic and resistance exercise and survival will be explored.

We hypothesise that men with mCRPC randomized to the supervised exercise arm will experience longer OS and time to disease progression, less symptomatic skeletal-related events, and progression of pain; less pain and opiate use; better physical function and quality of life; and more favorable levels of inflammatory, energy metabolism, and other metabolic biomarkers compared to those in the self-directed exercise arm.

METHODS

Study Design

This is a multi-national and multi-centred, randomised controlled phase III clinical trial (INTERVAL-GAP4) recruiting 866 men with mCRPC to determine if supervised high-intensity aerobic and resistance training with psychosocial support increases OS compared to printed exercise recommendations (self-directed exercise) with psychosocial support. Patients will be randomly assigned (1:1) to either supervised exercise or self-directed exercise following the provision of written informed consent, confirmation of clinical eligibility, and successful completion of screening assessments (Figure 1). This program design has been chosen as it would be unethical to ask men with advanced prostate cancer to abstain from exercise for a two-year period, owing to the documented health benefits of exercise in prostate cancer patients with early stage disease. Accordingly, men randomised to the control arm are free to engage in exercise under their own management (self-directed exercise), where changes in physical activity of both groups will be monitored.

This study is compliant with the Declaration of Helsinki (World Medical Association), and requires human research ethics approval by the Institutional Review Board of each participating site prior to site activation. The trial was prospectively registered on the 10th March, 2016 (https://clinicaltrials.gov/ct2/show/NCT02730338), prior to patient recruitment commencing, with the trial now recruiting.

Participants

Men with histologically documented adenocarcinoma of the prostate and progressive

systemic metastatic disease despite castrate levels of testosterone (<50 ng/dL) due to orchiectomy or LHRH agonist (defined as mCRPC), and who meet study inclusion (Table 1) and exclusion (Table 2) criteria will be recruited to the study. This patient population was chosen due to the median OS among men with mCRPC is 32[9] to 35[8] months, thus OS is a feasible outcome to examine within the budget and timeline of the proposed study when using mCRPC patients as the target population. At enrolment, patients can be either treatment naïve for mCRPC or on first line AR targeted therapy for mCRPC (i.e. abiraterone or enzalutamide) without evidence of progression. Patients will be required to remain on ADT with a GnRH agonist/antagonist for the duration of their involvement in the study or have had prior bilateral orchiectomy. At enrolment, patients may have received chemotherapy for hormone-sensitive stages of disease. Patients cannot have received chemotherapy for castrate-resistance status at enrolment. Patients are not permitted to be on any experimental therapies at enrolment, however patients may be treated with chemotherapy or any other therapies for mCRPC post-enrolment and randomisation.

Screening

Once referred to the trial through the patients' managing clinician, and consented to the trial by an independent research officer, patients will undergo a screening process to confirm eligibility, with baseline measures taken prior to randomisation and completion of baseline exercise testing, if eligible. Measures necessary to complete the multivariable nomogram (http://www.cancer.duke.edu/Nomogram/firstlinechemotherapy.html)[20] risk assessment are mandatory, including the presence of nodal, bone and/or visceral metastases; the use of opioid analgesics; Eastern Cooperative Oncology Group (ECOG) performance status (must be ≤ 1); and the collection of standard-of-care pathology (LDH; Albumin; Hemoglobin; ALP; Prostate-Specific Antigen, PSA) within 28 days prior to baseline assessments. Patients must have a Halabi nomogram risk of low or intermediate (<195)[20] to confirm clinical eligibility prior to attempting a symptom-limited, medically supervised Cardiopulmonary Exercise Test (CPET) with electrocardiogram (ECG) recording.

Patients who are currently participating in vigorous aerobic activity (> 60 minutes per week) and/or structured resistance training (≥ 2 days per week) will be excluded. Patients must have no known contraindications to high-intensity aerobic or resistance exercise as determined by their physicians. Following medical clearance, patients will be required to complete a series of baseline questionnaires and will attempt the symptom-limited CPET with ECG using a stationary, electronically-braked cycle ergometer. Patients who successfully

pass their CPET (*i.e.,* no cardiac abnormalities while achieving a maximal rating of perceived exertion (RPE ≥ 9 of the BORG10 scale) will have their study information reviewed by the Exercise Coordination Centre (Edith Cowan University, Perth, Australia; ECU) for suitability of exercise prescription within the INTERVAL-GAP4 program, with consideration given to the location, number, and severity of bone metastases; and the Study Coordination Centre (University of California San Francisco, California, USA; UCSF) to confirm all clinical and study eligibility requirements prior to randomisation and subsequent baseline testing.

Randomisation

Patients will be centrally randomised by the Study Coordination Centre in a ratio of 1:1 to the two study arms, using block randomization in random blocks of 2, 4, and 6, and stratified by site and treatment status (*i.e.,* abiraterone or enzalutamide, yes/no; and radium-223, yes/no) as these therapies have a proven effect on progression-free survival[8,9]. A research officer at the Study Coordination Centre (SCC) with no patient contact will be responsible for uploading the randomisation schedule into Research Electronic Data Capture (REDCap; a secure application for building and managing online surveys and databases). Site-based research coordinators will subsequently randomise patients through the REDCap system once approval from the SCC is received. Patients will not be informed of their group allocation until after the completion of their baseline visit to maintain the integrity of effort and results of assessments performed. At the baseline visit, participants will complete all remaining assessments including physical function tests (*i.e.* strength tests, and 400m walk test), fasting blood and first-void urine collection (*i.e.* for correlative studies and biorepository storage), and any remaining questionnaires. Patients randomised to the supervised exercise arm will be enrolled into an automated text messaging program to provide behavioural support, and participants in both arms will commence an automated newsletter education program, circulated at the beginning of each cycle, intended to provide psychosocial support and enhance quality of life.

Outcomes

Measurements

This trial is comprised of a 96-week on-treatment period, approximating two years (24 cycles with each cycle spanning 28 days), followed by a 3-year follow-up period. Assessments are conducted at baseline and at routine intervals throughout the on-treatment period (Table 3). After the on-treatment phase ends, patients will enter the follow-up phase of

the trial, where their medical records and death certificates will be reviewed quarterly to quantify the primary end-point of OS and pre-specified secondary endpoints.

Primary Endpoint

Overall Survival

Overall survival (OS) is the primary outcome of this RCT. It is a validated endpoint for the approval of new treatments in medicine, and feasible within the budget and timeline of the study as men with mCRPC have a median survival of 32 to 35 months.[8,9] Patients will be followed for death a minimum of 36 months after randomisation. OS will be measured from the time of randomisation until death. Medical records and death certificates will be reviewed every 3 months to obtain survival status. Country-specific mortality databases will also be searched annually; cause of death will be determined through review of medical and death records. Importantly, quantification of OS through review of medical records and death certificates reduces loss to follow-up and missing data.

Secondary Endpoints

Disease Progression

Disease progression will be examined through review of patient medical records every 6 cycles and measured by the treating physician based on PCWG-3[21] and RECIST 1.1[22] criteria, to determine and monitor specific indications of disease progression (Table 4). Time to disease progression will be measured from randomisation until the first of the following: first Computed Tomography (CT) or bone scan documenting disease progression, initiation of a new therapy for mCRPC (clinical progression), or first occurrence of a symptomatic skeletal-related event (SSE).

Symptomatic Skeletal-Related Events (SSE)

Time to the first occurrence of a SSE will be defined as the time from randomization to documentation of any of the following: 1) use of external beam radiation therapy to relieve bone pain, 2) occurrence of new symptomatic pathological bone fractures excluding asymptomatic compression fractures, 3) known spinal cord compression, 4) change in anti-neoplastic therapy to treat bone pain, or 5) surgical intervention to treat bone pain. This information will be determined through adverse event recordings, concomitant medication and treatment reviews, and patient medical record reviews.

Progression of Pain, Degree of Pain, and Opiate Use

Analgesic or opiate use will be assessed using the Brief Pain Inventory-Short Form (BPI-SF), the World Health Organization (WHO) analgesic scale, and medical record review at entry with a lead-in period of <28 days. The WHO analgesic scale will be completed every three cycles (and confirmed by medical review) with the BPI-SF administered every three cycles until Cycle 24 and annually thereafter.

Immune Status, Inflammation, Energy Metabolism, and Androgen Metabolism

Fasted serum, plasma, and buffy coat samples (26 ml per visit) and first-void urine will be collected (with 4 ml of urine aliquots stored) at Cycles 0, 6, 12, and 24. Serum and plasma aliquots will be used to interrogate a panel of markers associated with immune function and inflammation, such as Interleukin (IL1β, IL-2, IL-6), tumor necrosis factor (TNFα), adiponectin, and C-Reactive Protein (CRP). Energy metabolism will be investigated through markers including serum insulin, plasma glucose, C-peptide and insulin growth-like factor (IGF-1). Androgen metabolism will be explored through biomarkers including testosterone, dihydrotestosterone (DHT), androstenedione, dehydroepiandrosterone (DHEA), 17-hydroxyprogesterone, 17-hydroxypregnenolone, sex hormone binding globulin (SHBG) and progesterone using mass spectrometry. The study is funded to analyse immune, inflammation, energy metabolism markers at the four collection time points and androgen metabolism markers at Cycles 0 and 6. Samples will be stored in regional biorepositories across the globe throughout the trial in -80°C biomedical freezers prior to batch analyses at the completion of the trial, for all patients who provided consent for this to occur at randomisation.

Physical Function

Muscle strength will be assessed using a one-repetition maximum (1RM) test for chest press, leg press, seated row and/or leg extension, depending on the location and severity of any bone metastases (Table 5),[9,11,23] recorded in kilograms (kg). Functional performance will be assessed through the 400m walk test, recording time to completion (in seconds) with heart rate maximum (HRmax), average (HRavg) and recovery (HRR) quantified. Aerobic fitness will be assessed through a medically supervised Cardiopulmonary Exercise Test (CPET) to determine patient VO2peak ($LO_2.min^{-1}$ and $mlO_2kg.min^{-1}$) and maximum workload (Watts) during a successful CPET (RPE ≥ 9, using BORG10 scale).[24] Physical function assessments are performed every three to six cycles across the two-year on-trial

period as previously described (Table 3).[2,10]

Quality of Life

Quality of life is measured through questionnaires every three cycles, including the Functional Assessment of Cancer Therapy (FACT-G); Functional Assessment of Chronic Illness Fatigue subscale (FACIT-Fatigue); European Organization of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30); Expanded Prostate Cancer Index Composition (EPIC-26); EuroQOL five dimensions questionnaire (EQ5D); State-Trait Anxiety Inventory (STAI), Centre for Epidemiologic Studies Depression (CES-D); and Pittsburgh Sleep Quality Index (PSQI) questionnaire.

Program Safety

All adverse events (AE) will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, V4.0), and will be assessed at every exercise testing and training visit. AE's will also be collected in both groups once per month by telephone. AE type, severity, attribution (disease-related or exercise-related), expectedness, and timing will be recorded on case report forms. Serious Adverse Events (SAE) include events that may be life-threatening, require and/or prolong inpatient hospitalization, result in persistent or significant disability or incapacity, or result in death. Adverse events expected on-trial include bone pain, pathological skeletal fracture, musculoskeletal injury, joint pain, falls and/or muscle soreness. All patients regardless of group will require medical clearance following adverse events prior to re-commencing their exercise program.

Health Economics

An economic evaluation will be performed in parallel to the trial to assess the health benefits, additional costs, and potential savings of including exercise therapy as standard of care for men with mCRPC. This health economics protocol will inform the relative value for money of exercise medicine compared with other healthcare interventions in this patient population and stage of disease. Hospital resource consumption and associated costs will also be obtained to assess costs for secondary healthcare utilisation between the intervention and control groups (supervised exercise and self-directed exercise respectively). All hospital events, including emergency department attendances and admissions, outpatient visits and procedures, and inpatient admissions for all causes will be explored, to quantify and identify

potential disease-related (prostate cancer) events, as well as total healthcare resource use for all other purposes inclusive of comorbidities and other chronic diseases. The cost of providing the supervised exercise and self-managed intervention will also be quantified. Due to the international distribution of investigator sites involved this study, a regional (country by country) and global (pooled) analysis will be conducted to account for regional differences in healthcare systems, coverage and costs.

Data on health benefits and costs will be appropriately adjusted for covariates, such as age, common comorbidities (e.g. diabetes, cardiovascular disease) and body mass index (BMI). Health benefits will be measured using quality of life derived from the EQ5D and converted to a health utility scale using regional norms (where possible) to derive quality-adjusted life years (QALYs) for cost utility analysis. Given the duration of this multinational RCT, costs associated with health resource use and delivery of the supervised exercise intervention will be standardised to a common year. Incremental costs and benefits will be subsequently estimated and reported as an incremental cost effectiveness ratio (ICER), which will be bootstrapped[25] to identify 95% confidence intervals. This will be subsequently used to quantify the probability of whether the intervention is good value for money, and the level of risk for mCRPC patients not being 'better-off' by receiving supervised exercise (i.e. the intervention). Deterministic sensitivity analysis will be undertaken to identify the main drivers of the costs, outcomes, and value for money.

Patient Programs

Exercise Prescription

Patients assigned to the intervention arm will receive a 96-week, individualized (*i.e.* based on a needs analysis and physical assessment of patient condition and capacity), periodised (*i.e.* the systemic organization of exercise variation into microcycles (weekly), mesocycles (monthly) and macrocycles (annually)), progressive and autoregulated (*i.e.* patients progress at their own pace based on variations in health, performance capability, fatigue, recovery capacity, or scheduling commitments, with adjustments made each session according to patient capacity on the day of exercise training), consisting of structured resistance exercise and combinations of high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) aerobic exercise (Table 5 and Table 6). The initial 48 weeks of the program (Year 1) will be supervised in an exercise clinic setting, with a gradual tapered transition to self-management, and the subsequent 48 weeks of the program (Year 2)

will be self-managed with one exercise visit required at the beginning of each cycle (every 4 weeks). This exercise prescription critically utilises periodisation to maximise training stimulus and physiological adaptation while also reducing the risk of injury, overtraining or staleness;[11,26] and autoregulation to allow advanced mCRPC patients to self-determine their capabilities at each session collaboratively with the supervising clinical exercise physiologist, thereby lowering intensity or volume if the patient is fatigued or unwell; or raising intensity or volume if the patient is energetic and motivated.[11,26] Furthermore, the exercise program will be modified for any mCRPC patients with bone metastases depending on the size and location of metastases (Table 7), performed individually, or in small groups (of up to 4-6 patients per session).

Resistance exercise intensity is prescribed using the repetition maximum (RM) method, which is monitored and adjusted throughout the program, with weight increased or decreased as the patient becomes stronger or weaker (*i.e.,* 8RM refers to the highest amount of weight a patient can lift eight times per set). Resistance training repetitions will not be performed to the point of neuromuscular failure, but rather the set will be ceased 1 to 2 repetitions short of the patient being unable to complete a repetition. Performing resistance training sets to neuromuscular failure is unlikely to provide additional benefit in non-athlete populations.[27]

Aerobic exercise intensity is prescribed using the rating of perceived exertion (RPE) method, where aerobic ergometer resistance or speed will be adjusted to elicit the target RPE throughout the trial. A confirmatory, supervised aerobic assessment – the constant load test[24] will be conducted at the start of each cycle to monitor aerobic fitness progression across the exercise program including the self-management period. The constant load test (CLT) is a short, three-minute submaximal exercise test performed on a cycle ergometer at a pre-set workload (70% of achieved CPET workload at the screening visit), with a graded four minute warm-up, and active three minute unloaded cool down (*i.e.,* ten minutes total). This CLT workload established at baseline remains constant (unchanged) throughout the trial, and is used to assess program effectiveness with HRmax, HRavg, HRR and RPE recorded. Impact exercise is excluded from the exercise prescription for all patients as it is a contraindication for patients with bone metastases, comprising over 80% of mCRPC patients.

Behavioural Support

Patients assigned to the supervised exercise arm will also receive behavioural support to help promote program adherence and compliance when tapering to self-management.

Behavioural support is provided in text message format, the overarching focus of which will be to increase perceived control in task-specific exercises and assist patients with overcoming individual barriers to exercise, rooted in Social Cognitive Theory (SCT) and Theory of Planned Behaviour (TPB) constructs.[28-30] The level of behavioural support provided will increase as patient self-management increases, providing one text per week (Cycle 0), two texts per week (Cycles 1 to 8), three texts per week (Cycles 9 to 11) and five texts per week (Cycles ≥12). Some text messages will ask patients to provide a response in a return text message to heighten patient engagement.

Psychosocial Support

Psychosocial support will be provided to all patients in the trial. Participants will be given a digital or mailed two-to-three page newsletter each month, to provide education and information on topics relevant for men with advanced prostate cancer, including, but not limited to, staying healthy, lifestyle behaviours, goal setting, managing fatigue, bone health, side-effects of treatment, managing side-effects, depression, social support, pain management, sexual intimacy, cognitive changes and gaining control.

Self-directed Exercise Group (Control)

Patients randomised to the self-directed exercise group will receive the psychosocial support described above. In addition, these patients will also be provided with the current American College of Sports Medicine (ACSM) guidelines for physical activity for cancer survivors[31,32] and print information on how to pursue a self-directed exercise program.

This self-directed exercise strategy is being employed as it would be unethical to ask men with advanced prostate cancer to abstain from exercise for a two-year period, owing to the documented health benefits of exercise in prostate cancer patients with early stage disease. Similarly, this trial utilises a single-blinded study design where it is not possible to blind patients to the intervention, and given recruited patients are at the end-stage of life, the ability to provide supervised exercise to control patients after trial completion to optimise patient retention is not an option. Thus, it is felt the provision of printed material for self-directed exercise will assist with patient retention for men randomised to the control arm, whom are free to exercise as much or as little as they like.

There is considerable contrast in the effectiveness of a supervised program pursued in an exercise clinic versus home-based and self-directed formats; thus, we believe this design will differentiate the benefits of the exercise intervention for the primary and secondary

outcomes and maintain interventional fidelity in the trial. To date, research into unsupervised exercise programs in cancer populations have shown limited effectiveness.[33-35]

Statistical Considerations

Analysis will be performed using an intention-to-treat approach[36], powered to detect a hazard ratio (HR) of 0.78 for OS between patients randomised to the two treatment arms. Given a total enrolment period of 36 months, an on-trial period of 24 x 4-week cycles, a minimum 36 months follow-up after the on-treatment period; survival time following an exponential distribution; and a median OS of 33.5 months in the self-directed exercise arm, the estimated sample size required to detect a HR of 0.78 with 80% power at significance level of 0.05 is 824 (*i.e.* 412 men in each arm). Accounting for up to 5% of patients with missing data on OS, we aim to enroll 866 men (*i.e.* 433 men in each arm). Four interim analyses will be performed: feasibility (completed in 2016), intervention effectiveness (first 15% of patients following the 6 cycles using leg extension strength and 400m walk test data); efficacy (first 50% of patients following death to investigate OS); and accrual assessment (quarterly analysis).

Trial Management

INTERVAL-GAP4 has several levels of management to ensure the trial is appropriately governed and operational. The study protocol was established through a Protocol Development Working Group with guidance from a Steering Committee and Research Advisory Committee, each independent from each other, with globally recognised leaders in clinical and academic contexts pertaining to prostate cancer. Operationally, the INTERVAL-GAP4 trial is overseen by the Steering Committee, and co-managed by the Exercise Coordination Centre (ECC; Exercise Medicine Research Institute, Edith Cowan University, AU), the Study Coordination Centre (SCC; Department of Urology, University of California San Francisco, US), and the Global Project Manager (Global Action Plan, Movember Foundation, AU) with guidance from the Research Advisory Committee. The trial also has a Protocol Amendment Review Committee to continually evaluate protocol performance and review or approve proposed site-specific, investigator-led sub-studies.

INTERVAL-GAP4 has a Data Safety and Monitoring Board (DSMB) to oversee the data monitoring of the trial, and to monitor the safety of patients enrolled in the trial, which is completely independent of all other governing committees and site investigators. The trial also has a Medical Monitor Team consisting of several urologists and medical oncologists in

Canada, United Kingdom and United States of America. The SCC oversees site training, enrolment of patients (including randomisation), study databases, clinical data collection and data auditing, behavioural and psychosocial support programs, country-specific translations, AE and SAE reporting, liaison with the Medical Monitors and DSMB and implementation of central data collection software (REDCap, Vanderbilt University, Nashville, USA). The ECC oversees site training of exercise physiologists and professionals pertaining to exercise programming and supervision of advanced prostate cancer patients; oversees exercise testing and training, and delivery of the INTERVAL-GAP4 prescription; and manages exercise data collection, auditing and implementation of the exercise management software (PhysiTrack, Brighton, UK). The INTERVAL-GAP4 protocol has been approved by the Movember Research Advisory Committee, the Movember Board, and has been approved by the Human Research Ethics Committees of all sites currently open for recruitment. All data entered into REDCap and PhysiTrack are de-identified (*i.e.* using the patients' study identifier), with all forms uploaded to REDcap de-identified (*i.e.* all identifiable information is redacted).

Patient and Public Involvement

Movember Foundation is a charitable organisation advocating for improved outcomes for men with prostate cancer. As the funder of this global trial, with extensive consumer representative networks (*i.e.* patients, their families and their carers) across the globe, the organisation is uniquely positioned to represent the views and experiences of consumers in Australia, Canada, United Kingdom and the United States of America (among others) who have engaged with Movember's activities over the past fifteen years. This unique viewpoint and experience has been used to ensure that the study protocol engages participants in a respectful, ethical and impactful way, while addressing the needs of metastatic, castrate-resistant prostate cancer patients. Movember Foundation, with their consumer representative networks, will also facilitate the delivery of this study, by providing assistance with patient recruitment and support, as well as the translation and dissemination of the research findings to community members, patients and cancer support groups. In addition, the research team of this study protocol includes urologists and medical oncologists who work with the target population on a daily basis, from which these clinicians have used patient priorities, patient experience and patient preferences to help inform the development of the research questions and outcome measures. Lastly, the broader research team has conducted research studies in exercise and prostate cancer involving large quantities of participants over the course of the past 20 years, providing feedback to investigators to help design better exercise oncology

clinical trials. This sizeable patient interaction across the clinical and community landscape has contributed substantially to the design of this project.

ETHICS AND DISSEMINATION

Ethics approval was first obtained at Edith Cowan University (ID: 13236 NEWTON), with a further ten investigator sites in Australia, Canada, Europe, United Kingdom and United States since receiving site-specific human research ethics approval, prior to site activation and recruitment commencement. All future investigator sites joining the INTERVAL-GAP4 study are required to obtain site-specific human research ethics committee approvals, under-go site based education and training, and receive a site initiation visit prior to opening for recruitment. Future amendments to the protocol and associated documentation, if any, will be deliberated and approved by the Protocol Amendment Review Committee, followed by submission to, and approval of the Steering Committee. Approved amendments will be subsequently distributed to individual site investigators for submission to their human research ethics committees by the Study Coordination Centre.

Validation of exercise as medicine and its mechanisms of action will create evidence to change clinical practice. Accordingly, outcomes of this RCT will be published in international, high quality peer-reviewed journals, and presented at national and international conferences or research meetings. Outcomes of this study will also be delivered to community and consumer-led forums, and will be presented at local hospital departments and university seminars. Lastly, evidence derived from this RCT will be inserted into updated clinical exercise and/or medical guidelines and position statements within national and international governing bodies.

DISCUSSION

Preliminary evidence supports the potential beneficial role of exercise for prostate cancer survival. Exercise has potential as a low-toxicity adjuvant medicine that can be combined with standard cancer therapies to improve patient outcomes[11], with the exciting possibility of improving OS.[1] Data from observational epidemiological studies provide a convincing body of evidence to suggest a considerable survival benefit from habitual physical activity pre- and post-diagnosis in men with prostate cancer.[4,5,37-40] While these studies provide useful associations, they cannot infer or establish a causal relationship, and are subject to bias due to measurement error, unmeasured and residual confounding, reverse causation, and self-selection. Consequently, there is a need for RCTs to directly evaluate the

relationship between exercise (herein delivered as a tailored two-year exercise prescription) and OS in men with prostate cancer.[1,11] The INTERVAL-GAP4 protocol outlined in this paper aims to achieve this ambitious undertaking, and we hypothesize that a tailored, partially-supervised, structured, exercise intervention will deliver greater benefits than incidental or self-managed physical activity. This study is the first world-wide to explore the impact of exercise on OS in prostate cancer.

If it is demonstrated that this exercise intervention results in a clinically meaningful improvement in patient survival, then such exercise prescriptions can be immediately implemented worldwide, providing benefits to men with advanced prostate cancer. Further elucidation of the mechanisms by which exercise provides this survival benefit may inform the development of future therapeutic agents as well as improve the synergistic provision of exercise prescriptions in combination with existing therapies including chemotherapy, radiation therapy, enzalutamide and abiraterone.

Following protocol development and endorsement by the Steering Committee and Research Advisory Committee; the INTERVAL-GAP4 trial was launched in December 2015. Following trial launch, a pilot site in Perth, Western Australia (Edith Cowan University) was chosen to demonstrate protocol feasibility across the inaugural year (recruiting from March, 2016 to November, 2016); whereby the study protocol went through several iterations to enable minor amendments (from Version 1 to Version 4) under the guidance of a Protocol Amendment Review Committee, with Steering Committee oversight. Following the established feasibility and demonstration of the study protocol (with ten patients randomised at the pilot site in Year 1); along with the concurrent establishment of each trial coordination centre (SCC, ECC); investigator sites worldwide began to open for recruitment in January, 2017 in a staggered process, with six sites open mid-year (July, 2017), and a further five sites open by the end of the year (December, 2017). Remaining investigator sites are due to open within the subsequent 12 months (December, 2018) and additional sites are being considered.

CONCLUSIONS

Exercise is rapidly evolving as an emerging and provocative therapy in oncology, with excellent promise to meet the broad and magnified needs of advanced prostate cancer patients. In particular, exercise has the potential to delay disease progression and extend patient survival through numerous potential systemic and localised, mechanical and non-mechanical mechanisms. INTERVAL-GAP4 will be the first RCT to definitively examine if

supervised aerobic and resistance exercise increase OS among men with mCRPC compared to self-directed physical activity.

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FINANCIAL STATEMENT

This trial has been internationally funded by the Movember Foundation - a global charity organisation committed to the improvement of health outcomes for men living with prostate cancer as well as supporting men with testicular cancer and programs focused on suicide prevention and mental health. NHH is supported by a Cancer Council of Western Australia Research Fellowship.

CONFLICTS OF INTEREST

MB and SG are employees of Movember Foundation, who are the funders of this research.

CONTRIBUTORS

All authors contributed to the design and development of the INTERVAL-GAP4 protocol. Specifically, RUN, JMC, KSC, SPF, RG, DCH, LAM, SRP, MNP, SFEP, CJR and FS are members of the Steering Committee; with SAK, NHH, ELVB, EMG, OC, RUN and FS members of the Protocol Development and Protocol Amendment Review Committees. CJR, JC and FS are the study clinicians and acting medical monitors of the trial. All authors have contributed to writing, editing, review and approval of the study protocol, meeting the International Committee of Medical Journal Editors (ICMJE) recommendations.

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LEGEND OF FIGURES AND TABLES

Figure 1. Schematic overview of the INTERVAL-MCRPC trial.

Table 1. Inclusion Criteria.

Table 2. Exclusion Criteria.

Table 3. Summary of INTERVAL-MCRPC assessments.

Table 4. Criteria for the establishment of disease progression following randomisation.

Table 5. Exercise prescription for Cycle 0 (Weeks 1 to 4); a fully supervised introduction to exercise while incrementally building exercise capacity.

Table 6. Exercise prescription for Cycles 1 to 11 (Weeks 5 to 48); a progressive, periodised and autoregulated program with de-load weeks, tapering supervision to self-management.

Table 7. Modular, multimodal exercise programming for MCRPC patients with known bone metastases across resistance, aerobic and flexibility training based on lesion sites [9,11,22].

TABLE 1. Inclusion Criteria

Inclusion Criteria

• Histologically documented adenocarcinoma of the prostate with progressive systemic metastatic disease, despite castrate levels of testosterone (<50 ng/dL). Castrate levels of testosterone must be maintained while on study.
• At enrolment, patients may be clinically eligible through two pathways:
  ○ **Pathway A:** currently on abiraterone and/or enzalutamide and **not progressing**.
  ○ **Pathway B:** pre-abiraterone and pre-enzalutamide **with progressive disease**.
• Progressive disease must be demonstrated by one or more of the following criteria:
  1) Measureable disease progression:
  ▪ >20% increase in the sum of diameters of measurable lesions from the time of maximal regression; or the appearance of one or more new nodal, visceral or skeletal lesions).
  2) Bone scan progression:
  ▪ Appearance of one or more new lesions on a bone scan that is attributable to prostate cancer.
  3) PSA progression:
  ▪ PSA ≥ 2 ng/ml that has risen serially on at least two occasions, each at least one week apart (PSA1 < PSA2 < PSA3).
• Patients must be on androgen deprivation therapy (ADT) with a GnRH agonist / antagonist or prior bilateral orchiectomy. All patients are required to be on ADT during the study period.
• Receive a Halabi Nomogram score <195 [20], classified as low or intermediate risk.
• Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 1.
• Age ≥ 18 years.
• Be willing to travel to one of the exercise facilities for exercise testing and training.
• Be willing to use the technological aspects of the trial for patient monitoring and support.
• Fluent in the language designated by the institution where the patient will be enrolled.
• No major surgery ≤ 4 weeks at enrolment; and fully recovered from any prior surgery.
• Medical clearance to complete a symptom-limited cardiopulmonary exercise test (CPET) with electrocardiography (ECG), and to complete a structured and progressive resistance and aerobic exercise program of moderate-to-vigorous intensity.
• Must pass the CPET performed at screening (pre-enrolment), judged as achieving an RPE ≥ 9 on the 10-point BORG scale with no detected cardiac abnormalities. Patients with any abnormalities noted are permitted to enrol following cardiologist review and clearance.
• Meet the required baseline laboratory values: ANC ≥ 1500/uL; Platelet count ≥ 100,000/uL; Creatinine ≤ 1.5 x upper limits of normal; Bilirubin ≤ 1.5 x upper limits of normal; AST ≤ 1.5 x upper limits of normal; Serum testosterone ≤ 50 ng/dL
• Patients with bone metastases must be cleared by the Exercise Coordination Centre following review of their most recent bone scan to ensure they are able to participate in most exercises required by the trial.

TABLE 2. Exclusion Criteria

Exclusion Criteria
• No previous progression while on treatment with abiraterone and/or enzalutamide. • No prior chemotherapy for metastatic castrate-resistant prostate cancer. • Not currently receiving experimental treatment with non-approved drugs at enrolment. • No known brain metastases. • No known spinal cord compression, compromise or instrumentation due to metastatic disease. Radiation therapy for metastatic disease is allowed. • No moderate to severe bone pain (CTCAE v5.0 grading criteria). • No history of hypertension that is not well-controlled. • No congestive heart failure. • No recent serious cardiovascular events (within 12 months), including, but not limited to, transient ischemic attack, cerebrovascular accident, or myocardial infarction. • No medical condition, such as uncontrolled infection or cardiac disease, which in the opinion of the relevant physician, would make this protocol unreasonably hazardous for the patient. • No serious or non-healing wound, ulcer, or bone fracture. • Not experiencing shortness of breath, chest discomfort, or palpitations when performing activities of daily living. • Does not have chest pain generated by physical activity and has not developed chest pain in the previous month. • No peripheral neuropathy ≥ Grade 3 (CTCAE v5.0 grading criteria) • No psychiatric illness. • No small cell neuroendocrine tumours or pure small cell carcinoma of the prostate. • No current active second malignancy other than non-melanoma skin cancer. • Not participating in vigorous aerobic exercise for more than 60 minutes per week. • Not participating in structured resistance exercise for ≥ 2 sessions per week.

TABLE 3. Summary of INTERVAL-MCRPC assessments.

		On-Treatment Study Period (each cycle =28 days)																								Off-Treatment
	Screening	Cycle 0: Baseline	Supervised Exercise								Transition			Self-managed exercise program												Follow-up Period
Cycle		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Informed consent	X																										
Randomisation	X																										
Clinical History																											
Medical history[1]	X																									X	
Medication/Treatment history	X				X			X			X			X			X			X			X			X	
Body Measurements																											
Weight, waist, hip circumference, height (at baseline only)	X							X						X						X						X	
Lab Studies																											
CBC w/diff, blood chemistries	X							X						X													
Fasting lipid profile, fasting glucose, HbA1c		X						X																			
Efficacy																											
Overall survival, disease progression, symptomatic-skeletal event[2]								X						X						X						X	Twice yearly
WHO analgesic scale	X				X			X			X			X			X			X			X			X	Once yearly
Exercise testing – Supervised arm	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exercise testing – Self-directed arm		X						X						X						X						X	
Safety																											
Medical clearance	X							X						X						X						X	
Vital signs	X	X						X						X						X						X	
ECOG performance status	X				X			X			X			X			X			X			X			X	
Bone pain at exercise visits		Assessed at each supervised exercise visit using VAS																									
Adverse events[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Metabolic Research Studies																											

Research blood (fasting)		X						X					X											X	
FFPE tumour specimens		Request																							
Urine specimens		X						X					X											X	
Patient-Reported Outcomes																									
Demographics & health history questionnaire	X																								
Exercise screening questionnaire	X																								
Exercise, quality of life and memory questionnaires (3 or 6 month intervals, depending on survey)	X				X			X			X			X			X			X				X		X[4]
Food frequency questionnaire	X												X												X		

WHO: World Health Organization; ECOG: Eastern Cooperative Oncology Group; FFPE: formalin-fixed paraffin-embedded

[1]New conditions diagnosed on-study are recorded during the on-study period; [2]Per review of medical records or other documentation. Mortality data will be collected through medical records, death records, and other resources every 6 months during the on-treatment and follow-up periods. If the participant is lost to follow-up, we will contact next of kin or alternate contact. Death certificates will also be requested and all medical information pertaining to the death will be centrally reviewed to determine cause of death; [3]Continuously reported from informed consent until 28 days after Cycle 24, Day 1; [4]Selected assessments will be administered during the follow-up period on a yearly basis. If no response is received from the participant and medical records do not indicate death, we will follow up with next of kin or alternate contact.

TABLE 4. Criteria for the establishment of disease progression following randomisation.

Source	Criterion
Bone Scan	Appearance of ≥2 new lesions on bone scan, for bone scans that are completed >12 weeks following randomisation.
CT/MRI Scans	≥20% increase in the sum of lesion diameters, taking the reference as the smallest sum on study. In addition to this relative increase by 20%, the sum must also demonstrate: - an absolute increase >5mm, OR; - the appearance of one or more new lesions; OR - unequivocal progression of baseline non-measurable lesions.
MCRPC Therapy Initiation	Development of an indication for initiating a therapy for MCRPC after randomisation, including, but not limited to, abiraterone, enzalutamide, chemotherapy or radiation therapy.
Symptomatic Skeletal Events	Development of a symptomatic, skeletal related event (SSE) that must be attributable to disease.

Progression will be defined based on PCWG;-3 and RECIST 1.1 as all other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes 10-<15mm short axis) as well as truly non-measurable lesions. All non-measurable lesions will be recorded at baseline. If patients have measurable disease, there must be overall worsening in non-measurable disease such that the overall tumour burden has increased substantially. The designation of disease progression solely on the basis of change in non-measurable disease in the face of stable disease or partial response of the measurable disease is extremely rare.

TABLE 5. Exercise prescription for Cycle 0 (Weeks 1 to 4); a fully supervised introduction to exercise while incrementally building exercise capacity.

Period		Resistance Exercise	Aerobic Exercise
Cycle 0 (Week 1)	**Session 1**	1 set x 8RM x 6 exercises.	3 x 30 seconds at RPE (5). with 90 seconds recovery.
	Session 2		10 minutes at RPE (4). (*with 2 minute recovery as needed*).
	Session 3	1 sets x 12RM x 6 exercises.	3 x 30 seconds at RPE (5). with 90 seconds recovery.
Cycle 0 (Week 2)	**Session 1**	2 sets x 8RM x 6 exercises.	4 x 30 seconds at RPE (6). with 90 seconds recovery.
	Session 2		10 minutes at RPE (4). (*with 2 minute recovery as needed*).
	Session 3	2 sets x 120RM x 6 exercises.	4 x 30 seconds at RPE (6). with 90 seconds recovery.
Cycle 0 (Week 3)	**Session 1**	3 sets x 8RM x 6 exercises.	3 x 60 seconds at RPE (6). with 120 seconds recovery.
	Session 2		15 minutes at RPE (5). (*with 2 minute recovery as needed*).
	Session 3	3 sets x 12RM x 6 exercises.	3 x 60 seconds at RPE (6). with 120 seconds recovery.
Cycle 0 (Week 4 – De-load)	**Session 1**	2 sets x 8RM x 6 exercises.	3 x 30 seconds at RPE (6). with 90 seconds recovery.
	Session 2		10 minutes at RPE (4). (*with 2 minute recovery as needed*).
	Session 3	2 sets x 12RM x 6 exercises.	3 x 30 seconds at RPE (6). with 90 seconds recovery.
Additional Descriptions	INTERVAL-MCRPC prescription provides a gradually incremental introduction to the exercise program across Cycle 0 (Weeks 1 to 4). This familiarises and prepares patients for their subsequent participation in moderate-to-high load resistance exercise, as well as high-intensity interval and moderate-intensity continuous aerobic exercise. This cycle also contains a de-load week to increase recovery and promote adaptation prior to progressing into the full prescription. Program intensity is provided through a repetition maximum (RM) and rating of perceived exertion (RPE) system to support exercise autoregulation and patient management through-out cancer treatment and disease progression as needed [11].		

TABLE 6. Exercise prescription for Cycles 1 to 11 (Weeks 5 to 48); a progressive, periodised and autoregulated program with de-load weeks, tapering supervision to self-management.

Period		Resistance Exercise	Aerobic Exercise
Cycle 1 – 11 (Week 1)	**Session 1**	4 sets x 8RM x 6 exercises.	6 x 60 seconds at RPE (8). with 120 seconds recovery.
	Session 2		30 to 40 minutes at RPE (5). (*with 2 minute recovery as needed*).
	Session 3	4 sets x 12RM x 6 exercises.	6 x 60 seconds at RPE (8). with 120 seconds recovery.
Cycle 1 - 11 (Week 2)	**Session 1**	4 sets x 6RM x 6 exercises.	6 x 30 seconds at RPE (9). with 90 seconds recovery.
	Session 2		30 to 40 minutes at RPE (6). (*with 2 minute recovery as needed*).
	Session 3	4 sets x 10RM x 6 exercises.	6 x 30 seconds at RPE (9). with 90 seconds recovery.
Cycle 1 - 11 (Week 3)	**Session 1**	3 sets x 8RM x 6 exercises.	6 x 60 seconds at RPE (8). with 120 seconds recovery.
	Session 2		30 to 40 minutes at RPE (5). (*with 2 minute recovery as needed*).
	Session 3	3 sets x 12RM x 6 exercises.	6 x 60 seconds at RPE (8). with 120 seconds recovery.
Cycle 1 - 11 (Week 4 – De-load)	**Session 1**	2 sets x 6RM x 6 exercises.	4 x 30 seconds at RPE (6). with 90 seconds recovery.
	Session 2		30 to 40 minutes at RPE (4). (*with 2 minute recovery as needed*).
	Session 3	2 sets x 10RM x 6 exercises.	4 x 30 seconds at RPE (6). with 90 seconds recovery.
Additional Descriptions	INTERVAL-MCRPC prescription provides a periodised, progressive and individually tailored program consisting of moderate-to-high load resistance exercise, combined with high-intensity interval and moderate-intensity continuous aerobic exercise. Each cycle contains a de-load week to increase recovery and promote adaptation. Program intensity is provided through a repetition maximum (RM) and rating of perceived exertion (RPE) system to support exercise autoregulation through-out cancer treatment and disease progression as needed [11].		

TABLE 7. Modular, multimodal exercise programming for MCRPC patients with known bone metastases across resistance, aerobic and flexibility training based on lesion sites [9,11,22]

	Resistance			Aerobic		Flexibility
Metastases Site	**Upper**	**Trunk**	**Lower**	**WB**	**NWB**	**Static**
Pelvis	√	√	√**		√	√
Lumbar Spine	√		√		√	√***
Thoracic Spine / Ribs	√*		√	√	√	√***
Proximal Femur	√	√	√**		√	√
All Regions	√*		√**		√	√***

Note: √ = Target exercise region; * = exclusion of shoulder flexion/extension/abduction/adduction - inclusion of elbow flexion/extension; ** = exclusion of hip extension/flexion - inclusion of knee extension/flexion; WB = weight bearing (e.g. walking); NWB = non-weight bearing (e.g. cycling); *** = exclusion of spine/flexion/extension/rotation.

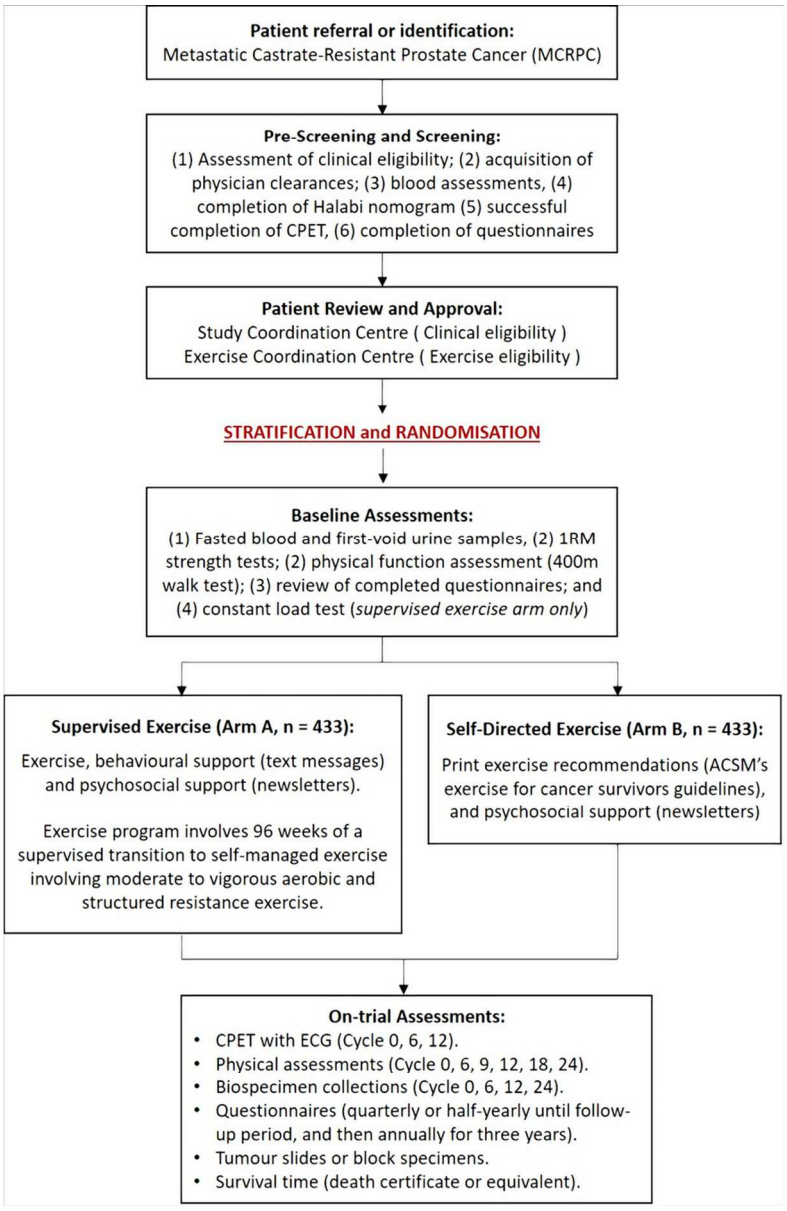

Figure 1. Schematic overview of the INTERVAL-MCRPC (GAP4) trial.

84x130mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 18
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15 and 16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	5 and 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	, 12, 13, 14
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7, Table 1 + 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	, 12, 13, 14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11, 14, 16,
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16,17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 8, 9, 10,11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, 10, 11, 12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12 and 13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15 and 16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15 and 16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15 and 16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 6 and 16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2 and 16
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

CERT ✓ Consensus on Exercise Reporting Template

A Checklist for what to include when reporting exercise programs

Section/Topic	Item #	Checklist item	Location **	
			Primary paper (page, table, appendix)	† Other (paper or protocol, website (URL)
WHAT: materials	1	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)	12 and 13	
WHO: provider	2	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor	3. 13. 15	
HOW: delivery	3	Describe whether exercises are performed individually or in a group	13	
	4	Describe whether exercises are supervised or unsupervised and how they are delivered	12. 13. 14	
	5	Detailed description of how adherence to exercise is measured and reported	16	
	6	Detailed description of motivation strategies	13. 14	
	7a	Detailed description of the decision rule(s) for determining exercise progression	12,13	
	7b	Detailed description of how the exercise program was progressed	12,13; Tables 5,6	
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)	N/A	
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)	12. 13. 14	
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)	13.14	
	11	Describe the type and number of adverse events that occurred during exercise	11	

WHERE: location	12	Describe the setting in which the exercises are performed	12. 13. 14	
WHEN, HOW MUCH: dosage	13	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc	12.13: Tables 5.6	
TAILORING: what, how	14a	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual	12.13: Tables 5.6	
	14b	Detailed description of how exercises are tailored to the individual	12.13: Tables 5.6	
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)	12.13: Tables 5.6	
HOW WELL: planned, actual	16a	Describe how adherence or fidelity to the exercise intervention is assessed/measured	12.13	
	16b	Describe the extent to which the intervention was delivered as planned	16	

BMJ Open

Intense exercise for survival among men with metastatic castrate-resistant prostate cancer (INTERVAL-GAP4): A multicentre, randomised, controlled phase III study protocol

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Sports and exercise medicine, Urology, Patient-centred medicine, Global health
Keywords:	physical activity, tumour biology, immune function, inflammation, disease progression

STUDY PROTOCOL

Intense exercise for survival among men with metastatic castrate-resistant prostate cancer (INTERVAL-GAP4): A multicentre, randomised, controlled phase III study protocol.

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Short Title: *Exercise and Survival of Prostate Cancer.*

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ABSTRACT

Introduction

Preliminary evidence supports the beneficial role of physical activity on prostate cancer outcomes. This phase III randomized controlled trial (RCT) is designed to determine if supervised high-intensity aerobic and resistance exercise increases overall survival in patients with metastatic castrate-resistant prostate cancer (mCRPC).

Methods and Analysis

Participants (n=866) must have histologically documented metastatic prostate cancer with evidence of progressive disease on androgen deprivation therapy (ADT; defined as mCRPC). Patients can be treatment naïve for mCRPC or on first line androgen receptor (AR)-targeted therapy for mCRPC (i.e. abiraterone or enzalutamide) without evidence of progression at enrolment; and with no prior chemotherapy for mCRPC. Patients will receive psychosocial support and will be randomly assigned (1:1) to either supervised exercise (high-intensity aerobic and resistance training) or self-directed exercise (provision of guidelines), stratified by treatment status and site. Exercise prescriptions will be tailored to each participant's fitness and morbidities. The primary endpoint is overall survival (OS). Secondary endpoints include time to disease progression, occurrence of a skeletal-related event, or progression of pain; and degree of pain, opiate use, physical and emotional quality of life, and changes in metabolic biomarkers. An assessment of whether immune function, inflammation, dysregulation of insulin and energy metabolism, and androgen biomarkers are associated with OS will be performed, and whether they mediate the primary association between exercise and OS will also be investigated. This study will also establish a biobank for future biomarker discovery or validation.

Ethics and Dissemination

Validation of exercise as medicine and its mechanisms of action will create evidence to change clinical practice. Accordingly, outcomes of this RCT will be published in international, peer-reviewed journals, and presented at national and international conferences. Ethics approval was first obtained at Edith Cowan University (ID: 13236 NEWTON), with a further ten investigator sites since receiving ethics approval, prior to activation.

KEY WORDS

physical activity, tumour biology, immune function, inflammation, disease progression

Trial Registration:

Prospectively registered, 10th March, 2016: https://clinicaltrials.gov/ct2/show/NCT02730338

STRENGTHS AND LIMITATIONS

- This is the first randomised controlled trial (RCT) to examine exercise and overall survival in men with prostate cancer.
- This is a novel multi-national, multi-centre and multidisciplinary RCT, with 24 months of supervised tapered to self-managed exercise with behavioural and psychosocial support, compared to self-directed exercise with psychosocial support alone, in men with metastatic castrate resistant prostate cancer (mCRPC).
- The study proposed will determine the efficacy of an individually tailored, progressive and autoregulated aerobic and resistance exercise program, supervised by accredited exercise physiologists (or equivalent) in addition to usual medical care; in parallel with a health economics analysis to assess the health benefits, additional costs, and potential savings of including exercise therapy as standard of care for men with mCRPC.
- The study has a translational team to investigate biomarkers associated with three candidate pathways: systemic inflammation, insulin/glucose metabolism, and androgen biosynthesis; to study how they mediate the association between exercise and overall survival, and to establish a blood, urine and tissue biobank for future biomarker discovery or validation.
- The outcomes of this Phase III RCT are limited to men with mCRPC.

INTRODUCTION

An emerging body of literature supports the role of exercise during cancer treatment as a therapy which leads to improved outcomes, both in quality of life and potentially disease control.[1] Identifying and evaluating low-toxicity adjuvant interventions, such as exercise, that can be combined with standard therapy to improve outcomes for men with prostate cancer is a high priority and has the potential to have a large impact on the clinical and public health burden of prostate cancer.

In 2006, Galvão, et al.[2] reported that resistance exercise and programs with resistance and aerobic exercise improved physical function and quality-of-life in men without metastases on androgen deprivation therapy (ADT) for prostate cancer. These results were expanded in a subsequent report Galvão et al.[3] showed that combined resistance and aerobic exercise reversed the loss of muscle mass and improved quality-of-life in prostate cancer patients on ADT. In addition, Kenfield et al.[4] reported that vigorous aerobic exercise after prostate cancer diagnosis was associated with a 60% lower risk of fatal prostate cancer and a 49% lower risk of all-cause mortality among men initially diagnosed with localized disease. The dose-specific effect of larger quantities of vigorous physical activity having greater survival benefit has also been reported by Friedenreich et al.[5] In addition, one prospective study reported that resistance exercise was associated with a 33% lower risk of all-cause mortality in male and female cancer survivors while overall physical activity was not.[6] These findings emphasize the potential benefits of exercise as an adjuvant treatment in prostate cancer. However, data on exercise and cancer survival to date have been from observational studies in which bias from confounding and reverse causation are of concern. Thus, a randomized controlled trial is needed to test whether exercise, in particular higher intensity aerobic exercise and resistance exercise, impacts overall survival in men with prostate cancer. Additionally, treatment-related fatigue is a common side effect in men with advanced prostate cancer and exercise may decrease fatigue and increase adherence to treatment regimens.[7-9]

While the prevailing view among patients and clinicians has been that exercise may be problematic for cancer patients with advanced disease, recent research has demonstrated tailored resistance and aerobic exercise to be well-tolerated, safe, and effective for improving physical structure and function.[10] Moreover, in patients with bone metastases, a highly tailored exercise prescription implementing a modular-multimodal approach and avoiding excessive loading of the skeletal lesions has been demonstrated to be safe and effective.[10]

There are many potential mechanisms by which exercise may lower risk of prostate cancer progression.[1,11,12] Exercise influences all hormonal systems in the body, including key hormones relevant to prostate cancer, such as testosterone, growth hormone, insulin and insulin-like growth factor-1 (IGF-I). The androgen receptor (AR) and its transactivation by ligand are one of the most important determinants of prostate cancer progression. Measurements of serum androgens (including its receptors and binding proteins) provide an important biomarker for the effectiveness of androgen deprivation and prostate cancer progression. The effects of exercise on serum androgen levels remain elusive to date,[13] with current studies limited by low patient numbers and inadequate methods for measuring testosterone levels in the low ranges seen in men on ADT.[14] This is especially true with the newer cyp17 inhibitors, such as abiraterone. Additionally, high levels of inflammatory biomarkers are associated with an increased risk of prostate cancer-specific mortality[15] and exercise is known to lower levels of circulating inflammatory biomarkers (e.g., IL-6) in elderly populations. [16,17] Increased physical activity may also produce epigenetic modulations that may inhibit tumor cell proliferation, such as altering histone deacetylase pathways. Exercise and dietary changes may also lower cholesterol, which epidemiological studies have suggested are associated with decreased risk of prostate cancer and progression of prostate cancer. [18,19] Together, these observations suggest that exercise interventions with prostate cancer patients may improve disease outcomes and quality of life. However, given the highly suggestive observational findings, a randomised control trial is warranted to establish clear causal relationships and guide clinical recommendations.

The primary objective of the GAP4 Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-GAP4) study is to determine if high-intensity aerobic and resistance training plus psychosocial support increase overall survival (OS) compared to self-directed exercise (non-supervised exercise recommendations) plus psychosocial support, in patients with metastatic, castrate-resistant prostate cancer (mCRPC). OS was chosen as the primary endpoint because it has clear biological, clinical, and public health significance and is a validated endpoint for approval of new treatments among men with mCRPC. Additionally, OS data can be obtained with minimal loss to follow-up through review of medical and death records.

Secondary objectives are to compare time to disease progression, time to first occurrence of a symptomatic skeletal-related event, time to progression of pain, degree of pain, and opiate use, physical and emotional quality of life, and change in levels of biomarkers of inflammation, energy metabolism, and androgen metabolism between the

supervised exercise and self-directed exercise groups. It will also be determined as to whether biomarkers of immune function, inflammation, energy metabolism, and androgen metabolism are associated with OS among men with mCRPC, and the extent to which these biomarkers mediate the hypothesized association between high-intensity aerobic and resistance exercise and survival will be explored.

We hypothesise that men with mCRPC randomized to the supervised exercise arm will experience longer OS and time to disease progression, less symptomatic skeletal-related events, and progression of pain; less pain and opiate use; better physical function and quality of life; and more favorable levels of inflammatory, energy metabolism, and other metabolic biomarkers compared to those in the self-directed exercise arm.

METHODS

Study Design

This is a multi-national and multi-centred, randomised controlled phase III clinical trial (INTERVAL-GAP4) recruiting 866 men with mCRPC to determine if supervised high-intensity aerobic and resistance training with psychosocial support increases OS compared to printed exercise recommendations (self-directed exercise) with psychosocial support. Patients will be randomly assigned (1:1) to either supervised exercise or self-directed exercise following the provision of written informed consent, confirmation of clinical eligibility, and successful completion of screening assessments (Figure 1). This program design has been chosen as it would be unethical to ask men with advanced prostate cancer to abstain from exercise for a two-year period, owing to the documented health benefits of exercise in prostate cancer patients with early stage disease. Accordingly, men randomised to the control arm are free to engage in exercise under their own management (self-directed exercise), where changes in physical activity of both groups will be monitored.

This study is compliant with the Declaration of Helsinki (World Medical Association), and requires human research ethics approval by the Institutional Review Board of each participating site prior to site activation. The trial was prospectively registered on the 10th March, 2016 (https://clinicaltrials.gov/ct2/show/NCT02730338), prior to patient recruitment commencing, with the trial now recruiting.

Participants

Men with histologically documented adenocarcinoma of the prostate and progressive

systemic metastatic disease despite castrate levels of testosterone (<50 ng/dL) due to orchiectomy or LHRH agonist (defined as mCRPC), and who meet study inclusion (Table 1) and exclusion (Table 2) criteria will be recruited to the study. This patient population was chosen due to the median OS among men with mCRPC is 32[9] to 35[8] months, thus OS is a feasible outcome to examine within the budget and timeline of the proposed study when using mCRPC patients as the target population. At enrolment, patients can be either treatment naïve for mCRPC or on first line AR targeted therapy for mCRPC (i.e. abiraterone or enzalutamide) without evidence of progression. Patients will be required to remain on ADT with a GnRH agonist/antagonist for the duration of their involvement in the study or have had prior bilateral orchiectomy. At enrolment, patients may have received chemotherapy for hormone-sensitive stages of disease. Patients cannot have received chemotherapy for castrate-resistance status at enrolment. Patients are not permitted to be on any experimental therapies at enrolment, however patients may be treated with chemotherapy or any other therapies for mCRPC post-enrolment and randomisation.

Screening

Once referred to the trial through the patients' managing clinician, and consented to the trial by an independent research officer, patients will undergo a screening process to confirm eligibility, with baseline measures taken prior to randomisation and completion of baseline exercise testing, if eligible. Measures necessary to complete the multivariable nomogram (http://www.cancer.duke.edu/Nomogram/firstlinechemotherapy.html)[20] risk assessment are mandatory, including the presence of nodal, bone and/or visceral metastases; the use of opioid analgesics; Eastern Cooperative Oncology Group (ECOG) performance status (must be ≤ 1); and the collection of standard-of-care pathology (LDH; Albumin; Hemoglobin; ALP; Prostate-Specific Antigen, PSA) within 28 days prior to baseline assessments. Patients must have a Halabi nomogram risk of low or intermediate (<195)[20] to confirm clinical eligibility prior to attempting a symptom-limited, medically supervised Cardiopulmonary Exercise Test (CPET) with electrocardiogram (ECG) recording.

Patients who are currently participating in vigorous aerobic activity (> 60 minutes per week) and/or structured resistance training (≥ 2 days per week) will be excluded. Patients must have no known contraindications to high-intensity aerobic or resistance exercise as determined by their physicians. Following medical clearance, patients will be required to complete a series of baseline questionnaires and will attempt the symptom-limited CPET with ECG using a stationary, electronically-braked cycle ergometer. Patients who successfully

pass their CPET (*i.e.,* no cardiac abnormalities while achieving a maximal rating of perceived exertion (RPE ≥ 9 of the BORG10 scale) will have their study information reviewed by the Exercise Coordination Centre (Edith Cowan University, Perth, Australia; ECU) for suitability of exercise prescription within the INTERVAL-GAP4 program, with consideration given to the location, number, and severity of bone metastases; and the Study Coordination Centre (University of California San Francisco, California, USA; UCSF) to confirm all clinical and study eligibility requirements prior to randomisation and subsequent baseline testing.

Randomisation

Patients will be centrally randomised by the Study Coordination Centre in a ratio of 1:1 to the two study arms, using block randomization in random blocks of 2, 4, and 6, and stratified by site and treatment status (*i.e.,* abiraterone or enzalutamide, yes/no; and radium-223, yes/no) as these therapies have a proven effect on progression-free survival[8,9]. A research officer at the Study Coordination Centre (SCC) with no patient contact will be responsible for uploading the randomisation schedule into Research Electronic Data Capture (REDCap; a secure application for building and managing online surveys and databases). Site-based research coordinators will subsequently randomise patients through the REDCap system once approval from the SCC is received. Patients will not be informed of their group allocation until after the completion of their baseline visit to maintain the integrity of effort and results of assessments performed. At the baseline visit, participants will complete all remaining assessments including physical function tests (*i.e.* strength tests, and 400m walk test), fasting blood and first-void urine collection (*i.e.* for correlative studies and biorepository storage), and any remaining questionnaires. Patients randomised to the supervised exercise arm will be enrolled into an automated text messaging program to provide behavioural support, and participants in both arms will commence an automated newsletter education program, circulated at the beginning of each cycle, intended to provide psychosocial support and enhance quality of life.

Outcomes

Measurements

This trial is comprised of a 96-week on-treatment period, approximating two years (24 cycles with each cycle spanning 28 days), followed by a 3-year follow-up period. Assessments are conducted at baseline and at routine intervals throughout the on-treatment period (Table 3). After the on-treatment phase ends, patients will enter the follow-up phase of

the trial, where their medical records and death certificates will be reviewed quarterly to quantify the primary end-point of OS and pre-specified secondary endpoints.

Primary Endpoint

Overall Survival

Overall survival (OS) is the primary outcome of this RCT. It is a validated endpoint for the approval of new treatments in medicine, and feasible within the budget and timeline of the study as men with mCRPC have a median survival of 32 to 35 months.[8,9] Patients will be followed for death a minimum of 36 months after randomisation. OS will be measured from the time of randomisation until death. Medical records and death certificates will be reviewed every 3 months to obtain survival status. Country-specific mortality databases will also be searched annually; cause of death will be determined through review of medical and death records. Importantly, quantification of OS through review of medical records and death certificates reduces loss to follow-up and missing data.

Secondary Endpoints

Disease Progression

Disease progression will be examined through review of patient medical records every 6 cycles and measured by the treating physician based on PCWG-3[21] and RECIST 1.1[22] criteria, to determine and monitor specific indications of disease progression (Table 4). Time to disease progression will be measured from randomisation until the first of the following: first Computed Tomography (CT) or bone scan documenting disease progression, initiation of a new therapy for mCRPC (clinical progression), or first occurrence of a symptomatic skeletal-related event (SSE).

Symptomatic Skeletal-Related Events (SSE)

Time to the first occurrence of a SSE will be defined as the time from randomization to documentation of any of the following: 1) use of external beam radiation therapy to relieve bone pain, 2) occurrence of new symptomatic pathological bone fractures excluding asymptomatic compression fractures, 3) known spinal cord compression, 4) change in anti-neoplastic therapy to treat bone pain, or 5) surgical intervention to treat bone pain. This information will be determined through adverse event recordings, concomitant medication and treatment reviews, and patient medical record reviews.

Progression of Pain, Degree of Pain, and Opiate Use

Analgesic or opiate use will be assessed using the Brief Pain Inventory-Short Form (BPI-SF), the World Health Organization (WHO) analgesic scale, and medical record review at entry with a lead-in period of <28 days. The WHO analgesic scale will be completed every three cycles (and confirmed by medical review) with the BPI-SF administered every three cycles until Cycle 24 and annually thereafter.

Immune Status, Inflammation, Energy Metabolism, and Androgen Metabolism

Fasted serum, plasma, and buffy coat samples (26 ml per visit) and first-void urine will be collected (with 4 ml of urine aliquots stored) at Cycles 0, 6, 12, and 24. Serum and plasma aliquots will be used to interrogate a panel of markers associated with immune function and inflammation, such as Interleukin (IL1β, IL-2, IL-6), tumor necrosis factor (TNFα), adiponectin, and C-Reactive Protein (CRP). Energy metabolism will be investigated through markers including serum insulin, plasma glucose, C-peptide and insulin growth-like factor (IGF-1). Androgen metabolism will be explored through biomarkers including testosterone, dihydrotestosterone (DHT), androstenedione, dehydroepiandrosterone (DHEA), 17-hydroxyprogesterone, 17-hydroxypregnenolone, sex hormone binding globulin (SHBG) and progesterone using mass spectrometry. The study is funded to analyse immune, inflammation, energy metabolism markers at the four collection time points and androgen metabolism markers at Cycles 0 and 6. Samples will be stored in regional biorepositories across the globe throughout the trial in -80°C biomedical freezers prior to batch analyses at the completion of the trial, for all patients who provided consent for this to occur at randomisation.

Physical Function

Muscle strength will be assessed using a one-repetition maximum (1RM) test for chest press, leg press, seated row and/or leg extension, depending on the location and severity of any bone metastases (Table 5),[9,11,23] recorded in kilograms (kg). Functional performance will be assessed through the 400m walk test, recording time to completion (in seconds) with heart rate maximum (HRmax), average (HRavg) and recovery (HRR) quantified. Aerobic fitness will be assessed through a medically supervised Cardiopulmonary Exercise Test (CPET) to determine patient VO2peak ($LO_2.min^{-1}$ and $mlO_2kg.min^{-1}$) and maximum workload (Watts) during a successful CPET (RPE ≥ 9, using BORG10 scale).[24] Physical function assessments are performed every three to six cycles across the two-year on-trial

period as previously described (Table 3).[2,10]

Quality of Life

Quality of life is measured through questionnaires every three cycles, including the Functional Assessment of Cancer Therapy (FACT-G); Functional Assessment of Chronic Illness Fatigue subscale (FACIT-Fatigue); European Organization of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30); Expanded Prostate Cancer Index Composition (EPIC-26); EuroQOL five dimensions questionnaire (EQ5D); State-Trait Anxiety Inventory (STAI), Centre for Epidemiologic Studies Depression (CES-D); and Pittsburgh Sleep Quality Index (PSQI) questionnaire.

Program Safety

All adverse events (AE) will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, V4.0), and will be assessed at every exercise testing and training visit. AE's will also be collected in both groups once per month by telephone. AE type, severity, attribution (disease-related or exercise-related), expectedness, and timing will be recorded on case report forms. Serious Adverse Events (SAE) include events that may be life-threatening, require and/or prolong inpatient hospitalization, result in persistent or significant disability or incapacity, or result in death. Adverse events expected on-trial include bone pain, pathological skeletal fracture, musculoskeletal injury, joint pain, falls and/or muscle soreness. All patients regardless of group will require medical clearance following adverse events prior to re-commencing their exercise program.

Health Economics

An economic evaluation will be performed in parallel to the trial to assess the health benefits, additional costs, and potential savings of including exercise therapy as standard of care for men with mCRPC. This health economics protocol will inform the relative value for money of exercise medicine compared with other healthcare interventions in this patient population and stage of disease. Hospital resource consumption and associated costs will also be obtained to assess costs for secondary healthcare utilisation between the intervention and control groups (supervised exercise and self-directed exercise respectively). All hospital events, including emergency department attendances and admissions, outpatient visits and procedures, and inpatient admissions for all causes will be explored, to quantify and identify

potential disease-related (prostate cancer) events, as well as total healthcare resource use for all other purposes inclusive of comorbidities and other chronic diseases. The cost of providing the supervised exercise and self-managed intervention will also be quantified. Due to the international distribution of investigator sites involved this study, a regional (country by country) and global (pooled) analysis will be conducted to account for regional differences in healthcare systems, coverage and costs.

Data on health benefits and costs will be appropriately adjusted for covariates, such as age, common comorbidities (e.g. diabetes, cardiovascular disease) and body mass index (BMI). Health benefits will be measured using quality of life derived from the EQ5D and converted to a health utility scale using regional norms (where possible) to derive quality-adjusted life years (QALYs) for cost utility analysis. Given the duration of this multinational RCT, costs associated with health resource use and delivery of the supervised exercise intervention will be standardised to a common year. Incremental costs and benefits will be subsequently estimated and reported as an incremental cost effectiveness ratio (ICER), which will be bootstrapped[25] to identify 95% confidence intervals. This will be subsequently used to quantify the probability of whether the intervention is good value for money, and the level of risk for mCRPC patients not being 'better-off' by receiving supervised exercise (i.e. the intervention). Deterministic sensitivity analysis will be undertaken to identify the main drivers of the costs, outcomes, and value for money.

Patient Programs

Exercise Prescription

Patients assigned to the intervention arm will receive a 96-week, individualized (*i.e.* based on a needs analysis and physical assessment of patient condition and capacity), periodised (*i.e.* the systemic organization of exercise variation into microcycles (weekly), mesocycles (monthly) and macrocycles (annually)), progressive and autoregulated (*i.e.* patients progress at their own pace based on variations in health, performance capability, fatigue, recovery capacity, or scheduling commitments, with adjustments made each session according to patient capacity on the day of exercise training), consisting of structured resistance exercise and combinations of high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) aerobic exercise (Table 5 and Table 6). The initial 48 weeks of the program (Year 1) will be supervised in an exercise clinic setting, with a gradual tapered transition to self-management, and the subsequent 48 weeks of the program (Year 2)

will be self-managed with one exercise visit required at the beginning of each cycle (every 4 weeks). This exercise prescription critically utilises periodisation to maximise training stimulus and physiological adaptation while also reducing the risk of injury, overtraining or staleness;[11,26] and autoregulation to allow advanced mCRPC patients to self-determine their capabilities at each session collaboratively with the supervising clinical exercise physiologist, thereby lowering intensity or volume if the patient is fatigued or unwell; or raising intensity or volume if the patient is energetic and motivated.[11,26] Furthermore, the exercise program will be modified for any mCRPC patients with bone metastases depending on the size and location of metastases (Table 7), performed individually, or in small groups (of up to 4-6 patients per session).

Resistance exercise intensity is prescribed using the repetition maximum (RM) method, which is monitored and adjusted throughout the program, with weight increased or decreased as the patient becomes stronger or weaker (*i.e.,* 8RM refers to the highest amount of weight a patient can lift eight times per set). Resistance training repetitions will not be performed to the point of neuromuscular failure, but rather the set will be ceased 1 to 2 repetitions short of the patient being unable to complete a repetition. Performing resistance training sets to neuromuscular failure is unlikely to provide additional benefit in non-athlete populations.[27]

Aerobic exercise intensity is prescribed using the rating of perceived exertion (RPE) method, where aerobic ergometer resistance or speed will be adjusted to elicit the target RPE throughout the trial. A confirmatory, supervised aerobic assessment – the constant load test[24] will be conducted at the start of each cycle to monitor aerobic fitness progression across the exercise program including the self-management period. The constant load test (CLT) is a short, three-minute submaximal exercise test performed on a cycle ergometer at a pre-set workload (70% of achieved CPET workload at the screening visit), with a graded four minute warm-up, and active three minute unloaded cool down (*i.e.,* ten minutes total). This CLT workload established at baseline remains constant (unchanged) throughout the trial, and is used to assess program effectiveness with HRmax, HRavg, HRR and RPE recorded. Impact exercise is excluded from the exercise prescription for all patients as it is a contraindication for patients with bone metastases, comprising over 80% of mCRPC patients.

Behavioural Support

Patients assigned to the supervised exercise arm will also receive behavioural support to help promote program adherence and compliance when tapering to self-management.

Behavioural support is provided in text message format, the overarching focus of which will be to increase perceived control in task-specific exercises and assist patients with overcoming individual barriers to exercise, rooted in Social Cognitive Theory (SCT) and Theory of Planned Behaviour (TPB) constructs.[28-30] The level of behavioural support provided will increase as patient self-management increases, providing one text per week (Cycle 0), two texts per week (Cycles 1 to 8), three texts per week (Cycles 9 to 11) and five texts per week (Cycles ≥12). Some text messages will ask patients to provide a response in a return text message to heighten patient engagement.

Psychosocial Support

Psychosocial support will be provided to all patients in the trial. Participants will be given a digital or mailed two-to-three page newsletter each month, to provide education and information on topics relevant for men with advanced prostate cancer, including, but not limited to, staying healthy, lifestyle behaviours, goal setting, managing fatigue, bone health, side-effects of treatment, managing side-effects, depression, social support, pain management, sexual intimacy, cognitive changes and gaining control.

Self-directed Exercise Group (Control)

Patients randomised to the self-directed exercise group will receive the psychosocial support described above. In addition, these patients will also be provided with the current American College of Sports Medicine (ACSM) guidelines for physical activity for cancer survivors[31,32] and print information on how to pursue a self-directed exercise program.

This self-directed exercise strategy is being employed as it would be unethical to ask men with advanced prostate cancer to abstain from exercise for a two-year period, owing to the documented health benefits of exercise in prostate cancer patients with early stage disease. Similarly, this trial utilises a single-blinded study design where it is not possible to blind patients to the intervention, and given recruited patients are at the end-stage of life, the ability to provide supervised exercise to control patients after trial completion to optimise patient retention is not an option. Thus, it is felt the provision of printed material for self-directed exercise will assist with patient retention for men randomised to the control arm, whom are free to exercise as much or as little as they like.

There is considerable contrast in the effectiveness of a supervised program pursued in an exercise clinic versus home-based and self-directed formats; thus, we believe this design will differentiate the benefits of the exercise intervention for the primary and secondary

outcomes and maintain interventional fidelity in the trial. To date, research into unsupervised exercise programs in cancer populations have shown limited effectiveness.[33-35]

Statistical Considerations

Analysis will be performed using an intention-to-treat approach[36], powered to detect a hazard ratio (HR) of 0.78 for OS between patients randomised to the two treatment arms. Given a total enrolment period of 36 months, an on-trial period of 24 x 4-week cycles, a minimum 36 months follow-up after the on-treatment period; survival time following an exponential distribution; and a median OS of 33.5 months in the self-directed exercise arm, the estimated sample size required to detect a HR of 0.78 with 80% power at significance level of 0.05 is 824 (*i.e.* 412 men in each arm). Accounting for up to 5% of patients with missing data on OS, we aim to enroll 866 men (*i.e.* 433 men in each arm). Four interim analyses will be performed: feasibility (completed in 2016), intervention effectiveness (first 15% of patients following the 6 cycles using leg extension strength and 400m walk test data); efficacy (first 50% of patients following death to investigate OS); and accrual assessment (quarterly analysis).

Trial Management

INTERVAL-GAP4 has several levels of management to ensure the trial is appropriately governed and operational. The study protocol was established through a Protocol Development Working Group with guidance from a Steering Committee and Research Advisory Committee, each independent from each other, with globally recognised leaders in clinical and academic contexts pertaining to prostate cancer. Operationally, the INTERVAL-GAP4 trial is overseen by the Steering Committee, and co-managed by the Exercise Coordination Centre (ECC; Exercise Medicine Research Institute, Edith Cowan University, AU), the Study Coordination Centre (SCC; Department of Urology, University of California San Francisco, US), and the Global Project Manager (Global Action Plan, Movember Foundation, AU) with guidance from the Research Advisory Committee. The trial also has a Protocol Amendment Review Committee to continually evaluate protocol performance and review or approve proposed site-specific, investigator-led sub-studies.

INTERVAL-GAP4 has a Data Safety and Monitoring Board (DSMB) to oversee the data monitoring of the trial, and to monitor the safety of patients enrolled in the trial, which is completely independent of all other governing committees and site investigators. The trial also has a Medical Monitor Team consisting of several urologists and medical oncologists in

Canada, United Kingdom and United States of America. The SCC oversees site training, enrolment of patients (including randomisation), study databases, clinical data collection and data auditing, behavioural and psychosocial support programs, country-specific translations, AE and SAE reporting, liaison with the Medical Monitors and DSMB and implementation of central data collection software (REDCap, Vanderbilt University, Nashville, USA). The ECC oversees site training of exercise physiologists and professionals pertaining to exercise programming and supervision of advanced prostate cancer patients; oversees exercise testing and training, and delivery of the INTERVAL-GAP4 prescription; and manages exercise data collection, auditing and implementation of the exercise management software (PhysiTrack, Brighton, UK). The INTERVAL-GAP4 protocol has been approved by the Movember Research Advisory Committee, the Movember Board, and has been approved by the Human Research Ethics Committees of all sites currently open for recruitment. All data entered into REDCap and PhysiTrack are de-identified (*i.e.* using the patients' study identifier), with all forms uploaded to REDcap de-identified (*i.e.* all identifiable information is redacted).

Patient and Public Involvement

Movember Foundation is a charitable organisation advocating for improved outcomes for men with prostate cancer. As the funder of this global trial, with extensive consumer representative networks (*i.e.* patients, their families and their carers) across the globe, the organisation is uniquely positioned to represent the views and experiences of consumers in Australia, Canada, United Kingdom and the United States of America (among others) who have engaged with Movember's activities over the past fifteen years. This unique viewpoint and experience has been used to ensure that the study protocol engages participants in a respectful, ethical and impactful way, while addressing the needs of metastatic, castrate-resistant prostate cancer patients. Movember Foundation, with their consumer representative networks, will also facilitate the delivery of this study, by providing assistance with patient recruitment and support, as well as the translation and dissemination of the research findings to community members, patients and cancer support groups. In addition, the research team of this study protocol includes urologists and medical oncologists who work with the target population on a daily basis, from which these clinicians have used patient priorities, patient experience and patient preferences to help inform the development of the research questions and outcome measures. Lastly, the broader research team has conducted research studies in exercise and prostate cancer involving large quantities of participants over the course of the past 20 years, providing feedback to investigators to help design better exercise oncology

clinical trials. This sizeable patient interaction across the clinical and community landscape has contributed substantially to the design of this project.

ETHICS AND DISSEMINATION

Ethics approval was first obtained at Edith Cowan University (ID: 13236 NEWTON), with a further ten investigator sites in Australia, Canada, Europe, United Kingdom and United States since receiving site-specific human research ethics approval, prior to site activation and recruitment commencement. All future investigator sites joining the INTERVAL-GAP4 study are required to obtain site-specific human research ethics committee approvals, under-go site based education and training, and receive a site initiation visit prior to opening for recruitment. Future amendments to the protocol and associated documentation, if any, will be deliberated and approved by the Protocol Amendment Review Committee, followed by submission to, and approval of the Steering Committee. Approved amendments will be subsequently distributed to individual site investigators for submission to their human research ethics committees by the Study Coordination Centre.

Validation of exercise as medicine and its mechanisms of action will create evidence to change clinical practice. Accordingly, outcomes of this RCT will be published in international, high quality peer-reviewed journals, and presented at national and international conferences or research meetings. Outcomes of this study will also be delivered to community and consumer-led forums, and will be presented at local hospital departments and university seminars. Lastly, evidence derived from this RCT will be inserted into updated clinical exercise and/or medical guidelines and position statements within national and international governing bodies.

DISCUSSION

Preliminary evidence supports the potential beneficial role of exercise for prostate cancer survival. Exercise has potential as a low-toxicity adjuvant medicine that can be combined with standard cancer therapies to improve patient outcomes[11], with the exciting possibility of improving OS.[1] Data from observational epidemiological studies provide a convincing body of evidence to suggest a considerable survival benefit from habitual physical activity pre- and post-diagnosis in men with prostate cancer.[4,5,37-40] While these studies provide useful associations, they cannot infer or establish a causal relationship, and are subject to bias due to measurement error, unmeasured and residual confounding, reverse causation, and self-selection. Consequently, there is a need for RCTs to directly evaluate the

relationship between exercise (herein delivered as a tailored two-year exercise prescription) and OS in men with prostate cancer.[1,11] The INTERVAL-GAP4 protocol outlined in this paper aims to achieve this ambitious undertaking, and we hypothesize that a tailored, partially-supervised, structured, exercise intervention will deliver greater benefits than incidental or self-managed physical activity. This study is the first world-wide to explore the impact of exercise on OS in prostate cancer.

If it is demonstrated that this exercise intervention results in a clinically meaningful improvement in patient survival, then such exercise prescriptions can be immediately implemented worldwide, providing benefits to men with advanced prostate cancer. Further elucidation of the mechanisms by which exercise provides this survival benefit may inform the development of future therapeutic agents as well as improve the synergistic provision of exercise prescriptions in combination with existing therapies including chemotherapy, radiation therapy, enzalutamide and abiraterone.

Following protocol development and endorsement by the Steering Committee and Research Advisory Committee; the INTERVAL-GAP4 trial was launched in December 2015. Following trial launch, a pilot site in Perth, Western Australia (Edith Cowan University) was chosen to demonstrate protocol feasibility across the inaugural year (recruiting from March, 2016 to November, 2016); whereby the study protocol went through several iterations to enable minor amendments (from Version 1 to Version 4) under the guidance of a Protocol Amendment Review Committee, with Steering Committee oversight. Following the established feasibility and demonstration of the study protocol (with ten patients randomised at the pilot site in Year 1); along with the concurrent establishment of each trial coordination centre (SCC, ECC); investigator sites worldwide began to open for recruitment in January, 2017 in a staggered process, with six sites open mid-year (July, 2017), and a further five sites open by the end of the year (December, 2017). Remaining investigator sites are due to open within the subsequent 12 months (December, 2018) and additional sites are being considered. This study protocol conforms to SPIRIT and CERT statements for RCTs and exercise reporting requirements. [41,42].

CONCLUSIONS

Exercise is rapidly evolving as an emerging and provocative therapy in oncology, with excellent promise to meet the broad and magnified needs of advanced prostate cancer patients. In particular, exercise has the potential to delay disease progression and extend patient survival through numerous potential systemic and localised, mechanical and non-

mechanical mechanisms. INTERVAL-GAP4 will be the first RCT to definitively examine if supervised aerobic and resistance exercise increase OS among men with mCRPC compared to self-directed physical activity.

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FINANCIAL STATEMENT

This trial has been internationally funded by the Movember Foundation - a global charity organisation committed to the improvement of health outcomes for men living with prostate cancer as well as supporting men with testicular cancer and programs focused on suicide prevention and mental health. NHH is supported by a Cancer Council of Western Australia Research Fellowship.

CONFLICTS OF INTEREST

MB and SG are employees of Movember Foundation, who are the funders of this research.

CONTRIBUTORS

All authors contributed to the design and development of the INTERVAL-GAP4 protocol. Specifically, RUN, JMC, KSC, SPF, RG, DCH, LAM, SRP, SFEP, CJR and FS are members of the Steering Committee; with SAK, NHH, EMG, ELVB, OC, RUN and FS members of the Protocol Development and Protocol Amendment Review Committees. CJR, JC and FS are the study clinicians and acting medical monitors of the trial. RUN, SAK, NHH, JMC, KSC, JC, SPF, RG, DCH, LAM, SRP, SFEP, EMG, ELVB, OC, MB, SG, LZ, DAG, CJR and FS collaboratively developed the study concept. RUN, NHH, SFEP, EMG, KSC and DAG designed the individualised, periodised and auto-regulated exercise prescription. KSC and DCH designed and developed the behavioural support elements of the study protocol. RG

and LZ produced statistical input, guidance and all calculations used in the study design. SAK, JMC and ELVB designed the data collection and management aspects of the protocol, and the psychosocial support materials for use. JC, SRP, CJR and FS established all clinical criterion, descriptions and design elements of the study. SPF, LAM and OC developed the translational and biomedical components of the protocol. SAK chaired the Protocol Development Working Group (PDWG), and along with NHH co-chaired the Protocol Amendment Review Committee (PARC) during the creation, optimisation and implementation of the study protocol. RUN and FS co-chaired the Steering Committee, overseeing the PDWG and PARC during this process. RUN, SAK, NHH, JMC, KSC, JC, SPF, RG, DCH, LAM, SRP, SFEP, EMG, ELVB, OC, MB, SG, LZ, DAG, CJR and FS contributed to writing, editing, review and approval of the study protocol, meeting the International Committee of Medical Journal Editors (ICMJE) recommendations.

DATA SHARING STATEMENT

All outcome data (primary and secondary) will be published in peer-reviewed clinical and academic journal articles, and/or presented at medical, clinical, academic or community conferences, seminars and/or meetings on an ongoing basis. Unpublished data, if any, can be requested at the conclusion of the trial through a written request to the Movember Foundation: info@movember.com

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LEGEND OF FIGURES AND TABLES

Figure 1. Schematic overview of the INTERVAL-MCRPC trial.

Table 1. Inclusion Criteria.

Table 2. Exclusion Criteria.

Table 3. Summary of INTERVAL-MCRPC assessments.

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Table 5. Exercise prescription for Cycle 0 (Weeks 1 to 4); a fully supervised introduction to exercise while incrementally building exercise capacity.

Table 6. Exercise prescription for Cycles 1 to 11 (Weeks 5 to 48); a progressive, periodised and autoregulated program with de-load weeks, tapering supervision to self-management.

Table 7. Modular, multimodal exercise programming for MCRPC patients with known bone metastases across resistance, aerobic and flexibility training based on lesion sites [9,11,22].

TABLE 1. Inclusion Criteria

Inclusion Criteria

• Histologically documented adenocarcinoma of the prostate with progressive systemic metastatic disease, despite castrate levels of testosterone (<50 ng/dL). Castrate levels of testosterone must be maintained while on study.
• At enrolment, patients may be clinically eligible through two pathways:
  ○ **Pathway A:** currently on abiraterone and/or enzalutamide and **not progressing**.
  ○ **Pathway B:** pre-abiraterone and pre-enzalutamide **with progressive disease**.
• Progressive disease must be demonstrated by one or more of the following criteria:
  1) Measureable disease progression:
  ▪ >20% increase in the sum of diameters of measurable lesions from the time of maximal regression; or the appearance of one or more new nodal, visceral or skeletal lesions).
  2) Bone scan progression:
  ▪ Appearance of one or more new lesions on a bone scan that is attributable to prostate cancer.
  3) PSA progression:
  ▪ PSA ≥ 2 ng/ml that has risen serially on at least two occasions, each at least one week apart (PSA1 < PSA2 < PSA3).
• Patients must be on androgen deprivation therapy (ADT) with a GnRH agonist / antagonist or prior bilateral orchiectomy. All patients are required to be on ADT during the study period.
• Receive a Halabi Nomogram score <195 [20], classified as low or intermediate risk.
• Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 1.
• Age ≥ 18 years.
• Be willing to travel to one of the exercise facilities for exercise testing and training.
• Be willing to use the technological aspects of the trial for patient monitoring and support.
• Fluent in the language designated by the institution where the patient will be enrolled.
• No major surgery ≤ 4 weeks at enrolment; and fully recovered from any prior surgery.
• Medical clearance to complete a symptom-limited cardiopulmonary exercise test (CPET) with electrocardiography (ECG), and to complete a structured and progressive resistance and aerobic exercise program of moderate-to-vigorous intensity.
• Must pass the CPET performed at screening (pre-enrolment), judged as achieving an RPE ≥ 9 on the 10-point BORG scale with no detected cardiac abnormalities. Patients with any abnormalities noted are permitted to enrol following cardiologist review and clearance.
• Meet the required baseline laboratory values: ANC ≥ 1500/uL; Platelet count ≥ 100,000/uL; Creatinine ≤ 1.5 x upper limits of normal; Bilirubin ≤ 1.5 x upper limits of normal; AST ≤ 1.5 x upper limits of normal; Serum testosterone ≤ 50 ng/dL
• Patients with bone metastases must be cleared by the Exercise Coordination Centre following review of their most recent bone scan to ensure they are able to participate in most exercises required by the trial.

TABLE 2. Exclusion Criteria

Exclusion Criteria
• No previous progression while on treatment with abiraterone and/or enzalutamide.
• No prior chemotherapy for metastatic castrate-resistant prostate cancer.
• Not currently receiving experimental treatment with non-approved drugs at enrolment.
• No known brain metastases.
• No known spinal cord compression, compromise or instrumentation due to metastatic disease. Radiation therapy for metastatic disease is allowed.
• No moderate to severe bone pain (CTCAE v5.0 grading criteria).
• No history of hypertension that is not well-controlled.
• No congestive heart failure.
• No recent serious cardiovascular events (within 12 months), including, but not limited to, transient ischemic attack, cerebrovascular accident, or myocardial infarction.
• No medical condition, such as uncontrolled infection or cardiac disease, which in the opinion of the relevant physician, would make this protocol unreasonably hazardous for the patient.
• No serious or non-healing wound, ulcer, or bone fracture.
• Not experiencing shortness of breath, chest discomfort, or palpitations when performing activities of daily living.
• Does not have chest pain generated by physical activity and has not developed chest pain in the previous month.
• No peripheral neuropathy ≥ Grade 3 (CTCAE v5.0 grading criteria)
• No psychiatric illness.
• No small cell neuroendocrine tumours or pure small cell carcinoma of the prostate.
• No current active second malignancy other than non-melanoma skin cancer.
• Not participating in vigorous aerobic exercise for more than 60 minutes per week.
• Not participating in structured resistance exercise for ≥ 2 sessions per week.

TABLE 3. Summary of INTERVAL-MCRPC assessments.

		On-Treatment Study Period (each cycle =28 days)																								Off-Treatment
	Screening	Cycle 0: Baseline	Supervised Exercise								Transition			Self-managed exercise program												Follow-up Period
Cycle		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Informed consent	X																										
Randomisation	X																										
Clinical History																											
Medical history[1]	X																									X	
Medication/Treatment history	X				X			X			X			X			X			X			X			X	
Body Measurements																											
Weight, waist, hip circumference, height (at baseline only)	X							X						X						X						X	
Lab Studies																											
CBC w/diff, blood chemistries	X							X						X													
Fasting lipid profile, fasting glucose, HbA1c		X						X																			
Efficacy																											
Overall survival, disease progression, symptomatic-skeletal event[2]								X						X						X						X	Twice yearly
WHO analgesic scale	X				X			X			X			X			X			X			X			X	Once yearly
Exercise testing – Supervised arm	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exercise testing – Self-directed arm		X						X						X						X						X	
Safety																											
Medical clearance	X							X						X						X						X	
Vital signs	X	X						X						X						X						X	
ECOG performance status	X				X			X			X			X			X			X			X			X	
Bone pain at exercise visits		Assessed at each supervised exercise visit using VAS																									
Adverse events[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Metabolic Research Studies																											

Research blood (fasting)		X					X					X											X	
FFPE tumour specimens		Request																							
Urine specimens		X					X					X											X	
Patient-Reported Outcomes																									
Demographics & health history questionnaire	X																								
Exercise screening questionnaire	X																								
Exercise, quality of life and memory questionnaires (3 or 6 month intervals, depending on survey)	X				X		X			X		X			X			X			X		X	X[4]
Food frequency questionnaire	X											X											X	

WHO: World Health Organization; ECOG: Eastern Cooperative Oncology Group; FFPE: formalin-fixed paraffin-embedded

[1]New conditions diagnosed on-study are recorded during the on-study period; [2]Per review of medical records or other documentation. Mortality data will be collected through medical records, death records, and other resources every 6 months during the on-treatment and follow-up periods. If the participant is lost to follow-up, we will contact next of kin or alternate contact. Death certificates will also be requested and all medical information pertaining to the death will be centrally reviewed to determine cause of death; [3]Continuously reported from informed consent until 28 days after Cycle 24, Day 1; [4]Selected assessments will be administered during the follow-up period on a yearly basis. If no response is received from the participant and medical records do not indicate death, we will follow up with next of kin or alternate contact.

TABLE 4. Criteria for the establishment of disease progression following randomisation.

Source	Criterion
Bone Scan	Appearance of ≥2 new lesions on bone scan, for bone scans that are completed >12 weeks following randomisation.
CT/MRI Scans	≥20% increase in the sum of lesion diameters, taking the reference as the smallest sum on study. In addition to this relative increase by 20%, the sum must also demonstrate: - an absolute increase >5mm, OR; - the appearance of one or more new lesions; OR - unequivocal progression of baseline non-measurable lesions.
MCRPC Therapy Initiation	Development of an indication for initiating a therapy for MCRPC after randomisation, including, but not limited to, abiraterone, enzalutamide, chemotherapy or radiation therapy.
Symptomatic Skeletal Events	Development of a symptomatic, skeletal related event (SSE) that must be attributable to disease.

Progression will be defined based on PCWG;-3 and RECIST 1.1 as all other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes 10-<15mm short axis) as well as truly non-measurable lesions. All non-measurable lesions will be recorded at baseline. If patients have measurable disease, there must be overall worsening in non-measurable disease such that the overall tumour burden has increased substantially. The designation of disease progression solely on the basis of change in non-measurable disease in the face of stable disease or partial response of the measurable disease is extremely rare.

TABLE 5. Exercise prescription for Cycle 0 (Weeks 1 to 4); a fully supervised introduction to exercise while incrementally building exercise capacity.

Period		Resistance Exercise	Aerobic Exercise
Cycle 0 (Week 1)	**Session 1**	1 set x 8RM x 6 exercises.	3 x 30 seconds at RPE (5). with 90 seconds recovery.
	Session 2		10 minutes at RPE (4). (*with 2 minute recovery as needed*).
	Session 3	1 sets x 12RM x 6 exercises.	3 x 30 seconds at RPE (5). with 90 seconds recovery.
Cycle 0 (Week 2)	**Session 1**	2 sets x 8RM x 6 exercises.	4 x 30 seconds at RPE (6). with 90 seconds recovery.
	Session 2		10 minutes at RPE (4). (*with 2 minute recovery as needed*).
	Session 3	2 sets x 120RM x 6 exercises.	4 x 30 seconds at RPE (6). with 90 seconds recovery.
Cycle 0 (Week 3)	**Session 1**	3 sets x 8RM x 6 exercises.	3 x 60 seconds at RPE (6). with 120 seconds recovery.
	Session 2		15 minutes at RPE (5). (*with 2 minute recovery as needed*).
	Session 3	3 sets x 12RM x 6 exercises.	3 x 60 seconds at RPE (6). with 120 seconds recovery.
Cycle 0 (Week 4 – De-load)	**Session 1**	2 sets x 8RM x 6 exercises.	3 x 30 seconds at RPE (6). with 90 seconds recovery.
	Session 2		10 minutes at RPE (4). (*with 2 minute recovery as needed*).
	Session 3	2 sets x 12RM x 6 exercises.	3 x 30 seconds at RPE (6). with 90 seconds recovery.
Additional Descriptions	INTERVAL-MCRPC prescription provides a gradually incremental introduction to the exercise program across Cycle 0 (Weeks 1 to 4). This familiarises and prepares patients for their subsequent participation in moderate-to-high load resistance exercise, as well as high-intensity interval and moderate-intensity continuous aerobic exercise. This cycle also contains a de-load week to increase recovery and promote adaptation prior to progressing into the full prescription. Program intensity is provided through a repetition maximum (RM) and rating of perceived exertion (RPE) system to support exercise autoregulation and patient management through-out cancer treatment and disease progression as needed [11].		

TABLE 6. Exercise prescription for Cycles 1 to 11 (Weeks 5 to 48); a progressive, periodised and autoregulated program with de-load weeks, tapering supervision to self-management.

Period		Resistance Exercise	Aerobic Exercise
Cycle 1 – 11 (Week 1)	**Session 1**	4 sets x 8RM x 6 exercises.	6 x 60 seconds at RPE (8). with 120 seconds recovery.
	Session 2		30 to 40 minutes at RPE (5). (*with 2 minute recovery as needed*).
	Session 3	4 sets x 12RM x 6 exercises.	6 x 60 seconds at RPE (8). with 120 seconds recovery.
Cycle 1 - 11 (Week 2)	**Session 1**	4 sets x 6RM x 6 exercises.	6 x 30 seconds at RPE (9). with 90 seconds recovery.
	Session 2		30 to 40 minutes at RPE (6). (*with 2 minute recovery as needed*).
	Session 3	4 sets x 10RM x 6 exercises.	6 x 30 seconds at RPE (9). with 90 seconds recovery.
Cycle 1 - 11 (Week 3)	**Session 1**	3 sets x 8RM x 6 exercises.	6 x 60 seconds at RPE (8). with 120 seconds recovery.
	Session 2		30 to 40 minutes at RPE (5). (*with 2 minute recovery as needed*).
	Session 3	3 sets x 12RM x 6 exercises.	6 x 60 seconds at RPE (8). with 120 seconds recovery.
Cycle 1 - 11 (Week 4 – De-load)	**Session 1**	2 sets x 6RM x 6 exercises.	4 x 30 seconds at RPE (6). with 90 seconds recovery.
	Session 2		30 to 40 minutes at RPE (4). (*with 2 minute recovery as needed*).
	Session 3	2 sets x 10RM x 6 exercises.	4 x 30 seconds at RPE (6). with 90 seconds recovery.
Additional Descriptions	INTERVAL-MCRPC prescription provides a periodised, progressive and individually tailored program consisting of moderate-to-high load resistance exercise, combined with high-intensity interval and moderate-intensity continuous aerobic exercise. Each cycle contains a de-load week to increase recovery and promote adaptation. Program intensity is provided through a repetition maximum (RM) and rating of perceived exertion (RPE) system to support exercise autoregulation through-out cancer treatment and disease progression as needed [11].		

TABLE 7. Modular, multimodal exercise programming for MCRPC patients with known bone metastases across resistance, aerobic and flexibility training based on lesion sites [9,11,22]

	Resistance			Aerobic		Flexibility
Metastases Site	**Upper**	**Trunk**	**Lower**	**WB**	**NWB**	**Static**
Pelvis	√	√	√**		√	√
Lumbar Spine	√		√		√	√***
Thoracic Spine / Ribs	√*		√	√	√	√***
Proximal Femur	√	√	√**		√	√
All Regions	√*		√**		√	√***

Note: √ = Target exercise region; * = exclusion of shoulder flexion/extension/abduction/adduction - inclusion of elbow flexion/extension; ** = exclusion of hip extension/flexion - inclusion of knee extension/flexion; WB = weight bearing (e.g. walking); NWB = non-weight bearing (e.g. cycling); *** = exclusion of spine/flexion/extension/rotation.

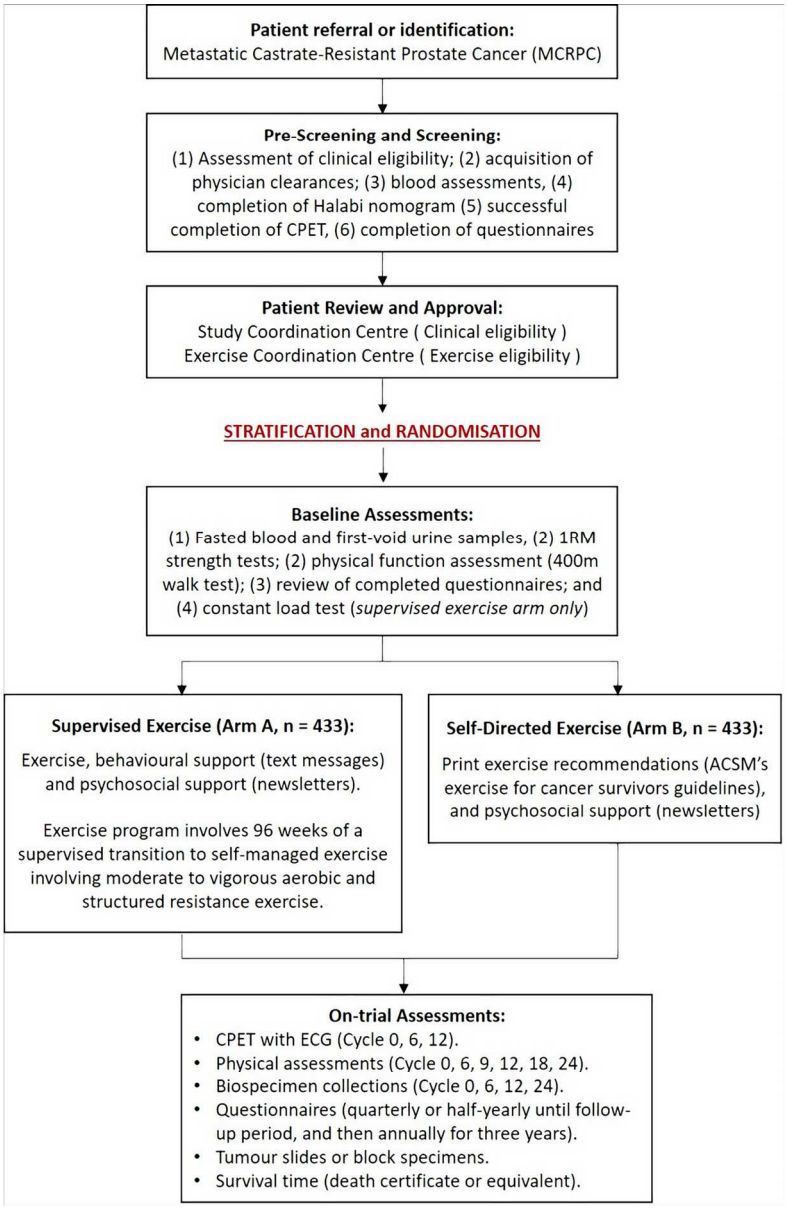

Figure 1. Schematic overview of the INTERVAL-MCRPC trial.

138x212mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 18
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15 and 16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	5 and 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	, 12, 13, 14
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7, Table 1 + 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	, 12, 13, 14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11, 14, 16,
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16,17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7, 8, 9, 10,11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, 10, 11, 12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12 and 13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15 and 16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15 and 16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15 and 16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 6 and 16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2 and 16
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

CERT ✓ Consensus on Exercise Reporting Template

A Checklist for what to include when reporting exercise programs

Section/Topic	Item #	Checklist item	Location **	
			Primary paper (page, table, appendix)	† Other (paper or protocol, website (URL)
WHAT: materials	1	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)	**12 and 13**	
WHO: provider	2	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor	**3. 13. 15**	
HOW: delivery	3	Describe whether exercises are performed individually or in a group	**13**	
	4	Describe whether exercises are supervised or unsupervised and how they are delivered	**12. 13. 14**	
	5	Detailed description of how adherence to exercise is measured and reported	**16**	
	6	Detailed description of motivation strategies	**13. 14**	
	7a	Detailed description of the decision rule(s) for determining exercise progression	**12,13**	
	7b	Detailed description of how the exercise program was progressed	**12,13; Tables 5,6**	
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations , video etc)	**N/A**	
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)	**12. 13. 14**	
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)	**13.14**	
	11	Describe the type and number of adverse events that occurred during exercise	**11**	

WHERE: location	12	Describe the setting in which the exercises are performed	**12. 13. 14**
WHEN, HOW MUCH: dosage	13	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc	**12.13: Tables 5.6**
TAILORING: what, how	14a	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual	**12.13: Tables 5.6**
	14b	Detailed description of how exercises are tailored to the individual	**12.13: Tables 5.6**
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)	**12.13: Tables 5.6**
HOW WELL: planned, actual	16a	Describe how adherence or fidelity to the exercise intervention is assessed/measured	**12.13**
	16b	Describe the extent to which the intervention was delivered as planned	**16**